EUROPEAN UNION (EU) RISK MANAGEMENT PLAN

FOR

BRINEURA (cerliponase alfa; BMN 190)

Date of Report

24 November 2023

BioMarin Pharmaceutical Inc.

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Novato, CA 94949 USA

RMP Version Number:	5.0
Data Lock Point for this RMP:	26 April 2022
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ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
CFR	Code of Federal Regulations
CLN2	also known as classical late-infantile neuronal ceroid lipofuscinosis [cLINCL], NCL2, or Jansky-Bielschowsky disease
CNS	central nervous system
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
ECG	Electrocardiogram
EEA	European Economic Area
EEG	Electroencephalogram
ERT	enzyme replacement therapy
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCP	Healthcare provider
HED	human equivalent dose
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
ICV	Intracerebroventricular
IND	Investigational New Drug (application)
IT	Intrathecal
IT-C	intrathecal-cisternal
IT-L	intrathecal-lumbar
KO	knock-out
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
QOW	every other week
PASS	Post-Authorisation Safety Study
PAES	Post-Authorisation Efficacy Study
PK	Pharmacokinetics
PL	Package leaflet
rhTPP1	recombinant human tripeptidyl peptidase-1
SAE	serious adverse event
SmPC	Summary of Product Characteristics
TPP1	tripeptidyl peptidase-1
US	United States
WT	wild-type

PART I: PRODUCT OVERVIEW

Active substance (INN or common name)	Cerliponase alfa
Pharmacotherapeutic group(s) (ATC Code)	Other alimentary tract and metabolism products, enzymes (A16AB17)
Marketing Authorisation Holder (or Applicant)	BioMarin International Limited Shanbally Ringaskiddy County Cork, Ireland
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Brineura
Marketing authorisation procedure	Centralised procedure
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (eg, origin of active substance of biological, relevant adjuvants or residues for vaccines)	Cerliponase alfa is a recombinant form of human tripeptidyl peptidase-1 (rhTPP1) and is produced in mammalian Chinese Hamster Ovary cells. As an Enzyme Replacement therapy (ERT), cerliponase alfa is given as an intracerebroventricular infusion to facilitate delivery of TPP1 widely to cells of the central nervous system, and expected to restore TPP1 activity, and reduce the accumulation of storage material.
Hyperlink to the product information	Module 1.3.1
Indication(s) in the EEA Current (if applicable)	Brineura is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.
Proposed (if applicable)	Not applicable

Dosage in the EEA Current (if applicable)	The recommended dose is 300 mg cerliponase alfa administered once every other week by intracerebroventricular infusion. In patients less than 2 years of age, lower doses are recommended; Brineura should be administered according to the following recommended dose once every other week: • Birth to < 6 months: 100 mg • 6 months to < 1 year: 150 mg • 1 year to < 2 years: 200 mg (first 4 doses), 300 mg (subsequent doses) • ≥ 2 years: 300 mg
Proposed (if applicable)	Not applicable
Pharmaceutical form(s) and strengths Current (if applicable)	Each vial of Brineura contains 150 mg of cerliponase alfa* in 5 ml of solution. Each ml of solution for infusion contains 30 mg of cerliponase alfa. * Cerliponase alfa is produced in mammalian Chinese Hamster Ovary cells. Clear to slightly opalescent and colourless to pale yellow solution, that may occasionally contain thin translucent fibres or opaque particles.
Proposed (if applicable)	Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the indication and target population

Indication – CLN2 disease (also known as TPP1 deficiency, classical late-infantile neuronal ceroid lipofuscinoses [cLINCL], NCL2, or Jansky-Bielschowsky disease)

Incidence:

CLN2 disease is a rare genetic disorder characterized by the deficiency of tripeptidyl peptidase-1 (TPP1) caused by mutations in the *CLN2* gene. Most epidemiological studies of CLN2 disease originated before molecular diagnosis and suggest an estimated incidence in the range of 0.15 to 0.78 per 100,000 live births in European countries including Portugal, Germany, Czech Republic and the United Kingdom (Claussen 1992; Teixeira 2003; Poupetova 2010; Williams 2011). Reported incidence in selected geographic regions of Canada is higher than those in Europe (2.2 to 9.0 per 100,000 live births) (MacLeod 1976; Moore 2008).

Prevalence:

The estimated population prevalence of CLN2 disease ranges from 0.15 to 0.75 per million in western European countries (Williams 2011); while observed prevalence in Scandinavia is slightly higher at 0.54 to 0.7 per million population (Uvebrant 1997; Williams 2011).

Demographics of the population in the authorised/proposed indication (age, gender, racial and/or ethnic origin) and risk factors for the disease:

There is limited information available on the demographic distribution of neuronal ceroid lipofuscinosis (NCL), also called Batten disease. While the prevalence of CLN2 varies worldwide, CLN2 prevalence is highest in Scandinavia and parts of Canada which has been attributed to small population and relative high amounts of parental consanguinity (Simpson 2014; Moore 2008).

Main existing treatment options:

The only disease modifying treatment option is Brineura (cerliponase alfa; BMN 190). Brineura is an enzyme-replacement therapy (ERT) that was approved for marketing in the United States on 27 April 2017 and in the European Union on 30 May 2017 for the treatment of patients with CLN2 disease (tripeptidyl-peptidase-1 [TPP1] deficiency). CLN2 patients also receive supportive care - symptomatic alleviation of seizures (anticonvulsants), motor control loss (bracing or wheelchairs), and feeding (gastrostomy tube).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

As a result of TPP1 enzyme deficiency, lysosomal storage material accumulation in the CNS is associated with neurodegeneration and, ultimately, death in late childhood to early adolescence. The onset of symptoms is typically between the ages of 2 and 4 years old (Kurachi 2000; Chang 2011; Nickel 2018) with an average age of diagnosis of 5 years. Patients with CLN2 disease typically present initially with seizures and a history of language delay, followed by ataxia, myoclonus, impaired speech, cognitive impairment, and developmental regression. The seizures and myoclonus, as well as other movement disorders, are intractable and difficult to control. A decline in vision and motor skills follows with patients becoming blind and wheelchair bound by approximately 6 years of age. Swallowing also becomes impaired and patients become G tube dependent for feeding and have a high risk of aspiration. Patients enter into a vegetative state and become fully dependent on their caregivers during the later stages of the disease. The majority of individuals with CLN2 disease present with the classic late-infantile phenotype, which has a rapidly progressing and predictable clinical course, with death typically occurring between the age of 5 years and mid-adolescence (Steinfeld 2002*;* Williams 2006). As with other enzyme deficiencies, CLN2 disease has a spectrum of phenotypes; the other atypical phenotypes are less common. Atypical phenotypes are associated with earlier or later symptom onset, variable symptoms and/or slower rate of progression, but still lead to neurodegeneration and premature death (Kohan 2013; Sun 2013; DiGiacopo 2015).

Important co-morbidities:

Co-morbidities of CLN2 relate to the condition itself and reflect the progression of the disease. Other than the conditions discussed above, a review of the literature did not reveal any other comorbidities occurring in this patient population.

Module SII: Non-clinical part of the safety specification

The nonclinical program consists of one in vitro study in TPP1 deficient fibroblasts, and 8 in vivo studies, including 3 single-dose studies in beagles and monkeys, and 5 repeat-dose studies in TPP1 KO mouse, and TPP1-null and WT Dachshund dogs. These studies are summarized in Table 1 below.

The safety and efficacy profile of cerliponase alfa, as assessed in the nonclinical program, supports the chronic ICV administration of cerliponase alfa at doses up to 960 mg administered every other week to CLN2 pediatric patients.

Table 1: Cerliponase Alfa Nonclinical Study Overview

Study Description and Number	Test System	Testing Site	Route (Inf. Duration)	Dose, Duration, and Administration Schedule	Parameters Evaluated	GLP	Study Status
PRIMARY PHARMACODYNAMICS							
Cellular Uptake Determination of BMN 190 in TPP1-Deficient Human Fibroblasts (TR-00195)	TPP1-deficient fibroblasts	BioMarin Pharmaceutical Inc.	*In vitro*		Activity K_{uptake}	No	Complete
SINGLE DOSE STUDIES							
Single Intrathecal Cisternal (IT-C) Administration CNS Distribution Study 0190-08-034	Beagle	Covance, Madison, WI	IT-C	8, 33, or 128 mg, 1-4 day recovery	Gross pathology CNS distribution CNS, liver, plasma, urine, and CSF TPP1 activity	No	Complete
Single Intracerebroventricular (ICV) Administration Toxicity, Toxicokinetic and CNS Distribution Study (0190-09-071) (Vuillemenot, 2014)	Cynomolgus monkey	Northern Biomedical Research, Muskegon, MI	ICV (~4 hr)	5, 14, or 20 mg, 3, 7, or 14 day recovery	Toxicity CSF/plasma immunogenicity CSF/plasma TK CNS distribution ECG	Yes[a]	Complete
Single Intrathecal Lumbar (IT-L) Administration Toxicity, Toxicokinetic and CNS Distribution Study (BMN190-11-046)	Cynomolgus monkey	Northern Biomedical Research, Muskegon, MI	IT-L (~4 hr)	14 mg, 3 day recovery	Toxicity CSF/plasma TK CNS distribution	No	Complete
REPEAT DOSE STUDIES							
Repeat IT-L Administration Pharmacology Study (BMN190-12-010) Reference: (Xu 2011)	TPP1 KO mouse	University of Medicine and Dentistry of New Jersey, Piscataway, NJ	IT-L	3 daily doses of 0.27 mg given to 15 week old mice 3 daily doses of 0.4 mg given to 4 week old mice	CNS enzyme activity Lysosomal storage material Gait analysis Lifespan	No	Complete

Study Description and Number	Test System	Testing Site	Route (Inf. Duration)	Dose, Duration, and Administration Schedule	Parameters Evaluated	GLP	Study Status
Three Month Repeat IT-C Administration Toxicity, CNS Distribution and Pharmacology Study (0190-09-066) Reference: Vuillemenot, 2011	TPP1-null and WT Dachshund dog (4 months old)	University of Missouri, Columbia, MO	IT-C (bolus)	32 mg, monthly for 3 months	Toxicity Plasma TK CNS distribution CSF/plasma immunogenicity Neurological, visual, and cognitive function Brain MRI EEG Lysosomal storage material	No	Complete
Nine Month Repeat Intracerebroventricular Administration Pharmacology, Toxicity and Toxicokinetic Study in Wild-type and TPP1-null Dachshund Dogs (0190-10-077) (Vuillemenot, 2014)	TPP1-null and WT Dachshund dog (2.5 months old)	University of Missouri, Columbia, MO	ICV, IT-L, and IT-C[b] (~2 or 4 hr)	0, 4, or 16 mg, every other week for at least 9 months	CSF/plasma clinical pathology Gross and microscopic pathology CSF/plasma immunogenicity CSF/plasma PK CNS distribution Neurological, visual, and cognitive function Brain MRI Lifespan extension Lysosomal storage material	No	Complete
Forty-Four Week Biweekly Intracerebroventricular (ICV) Infusion Study of BMN 190 in a Dachshund Model of CLN2 (BMN190-12-009) (Katz, 2014)	TPP1-null Dachshund dog (2.5 months old)	University of Missouri, Columbia, MO	ICV, IT-L,and IT-C[b] (~4 hr)	Up to 48 mg[c] every other week for up to 18 months	CSF/plasma clinical pathology Gross and microscopic pathology CSF/plasma PK CNS distribution Neurological, visual, and cognitive function Brain MRI Lifespan extension	No	Complete

Study Description and Number	Test System	Testing Site	Route (Inf. Duration)	Dose, Duration, and Administration Schedule	Parameters Evaluated	GLP	Study Status
Thirty-nine week Intracerebroventricular (ICV) Infusion Study of BMN 190 in a Dachshund Model of CLN2 (BMN190-12-027)	TPP1-null and WT Dachshund dog (4 months old)	University of Missouri, Columbia, MO	ICV, IT-L and IT-C[b] (~4 hr)	Up to 16 mg[d] every other week for up to 6 months	CSF/plasma clinical pathology Gross and microscopic pathology CSF/plasma PK Neurological, visual, and cognitive function Brain MRI ECG Lifespan extension	No	Complete

CNS, central nervous system; CSF, cerebrospinal fluid, CV, cardiovascular; ECG, electrocardiogram; EEG, electroencephalogram; GLP, Good Laboratory Practices; ICV, intracerebroventricular; IT-C, intrathecal-cisternal; IT-L, intrathecal-lumbar; KO, knock out; MRI, magnetic resonance imaging; TPP1, tripeptidyl peptidase-1; WT, wild- type

[a]Conducted in compliance with United States Food and Drug Administration (FDA) Good Laboratory Practice Regulations (GLP) (21 CFR, Part 58), the Japanese Ministry of Health, Labor, and Welfare (MHLW) Good Laboratory Practice Standards Ordinance 21, and the Organisation for Economic Co-operation and Development Principles of Good Laboratory Practice, ENV/MC/CHEM (98) 17.

[b]ICV/IT catheters have a limited patency in dogs. The ICV infusion route was used as long as the ICV catheters remained patent. If the ICV catheter was no longer patent, then the IT-L infusion route was used. If the IT-L catheter was no longer patent, then IT-C bolus administration was used.

[c]Due to infusion associated reactions that occurred after 48 mg dose #2 or #3, dose level was reduced to 2 mg and gradually increased back to 48 mg over 4 months to tolerize animals to cerliponase alfa

[d]Due to infusion associated reactions that occurred after repeat administration at the 16 mg, dose level was reduced to 2 mg and gradually increased to tolerize animals to cerliponase alfa.

The following summarizes key safety findings from non-clinical studies and their relevance to human usage.

Toxicity

Key issues identified from acute or repeat-dose toxicity studies

- Inflammation associated with long-term catheter placement and/or administration of exogenous protein

Reproductive/developmental toxicity

- Not evaluated

Genotoxicity

- Not evaluated

Carcinogenicity

- Not evaluated

Safety Pharmacology

Cardiovascular system, including potential effects on the QT interval

- Not observed in non-clinical studies

Nervous system

- Not observed in non-clinical studies

Nephrotoxicity and Hepatotoxicity

- Not observed in non-clinical studies

Other toxicity-related information or data

Nonclinical studies revealed four main findings:

1. delivery device-related inflammation in monkeys and Dachshund dogs adjacent to the CNS catheters and infusion site;
2. detection of anti-cerliponase alfa antibodies in plasma and cerebrospinal fluid (CSF) in WT and TPP1-null Dachshund dogs after repeat administration;
3. hypersensitivity reactions in Dachshund dogs after repeat dosing with the heterologous human protein; and
4. drop in plasma exposure after repeat dosing, with an apparent maintenance of CSF cerliponase alfa concentrations and a dose-dependent CNS tissue distribution.

Anti-cerliponase alfa antibodies were first detected in dogs administered cerliponase alfa by ICV infusion by Day 14 and Day 29 in plasma and CSF, respectively. Anti-cerliponase alfa titers increased over time until approximately Day 100, then remained stable for the

remainder of the study. Titer ranges in the CSF and plasma were similar. The presence of antibodies correlated with a decrease in cerliponase alfa exposure in the plasma of 4 and 16 mg treated animals by Dose 10. However, the presence of anti-cerliponase alfa antibodies in the CSF did not appear to correlate with a reduction in CSF drug levels by Dose 10 in animals treated with 16 mg of cerliponase alfa.

Scaling from the dog to the human equivalent dose (HED) was based on a 20:1 ratio between human and Dachshund dog brain mass. An average brain mass of 1000 g was used in calculations. The no-observed-adverse-effect level (NOAEL) of 48 mg from the repeat-dose dog studies yields a HED of 960 mg when scaled for brain weight.

Based on these findings, no additional non-clinical studies are planned.

Module SIII: Clinical trial exposure

During development, a total of 24 patients with CLN2 were enrolled in Study 190-201; 23 of these 24 patients continued with enrollment in Study 190-202 and a total of 14 patients with CLN2 were enrolled in Study 190-203. All participants received at least one dose of cerliponase alfa.

Cumulative participant exposure is represented in Table SIII.1. Clinical trial exposure is defined as any participant who received at least 1 dose of cerliponase alfa during the study. Analysis of cumulative exposure data by age group and sex, dose, and racial group is provided in Table SIII.2, Table SIII.3, and Table SIII.4.

Summaries of the patients enrolled in 190-201/202 and 190-203 by duration of exposure in 190-201, 190-202 and 190-203, dose, age group, and gender are provided below

Table SIII.1: Cumulative Participant Exposure to Brineura in Clinical Trials

Trial Number	Dose Received	Number of Participants
190-201	30 mg QOW	3
	100 mg QOW	6
	300 mg QOW	24
190-202	300 mg QOW	23
190-203	200 mg QOW	5
	300 mg QOW	14

Totals	
190-201/202	24
190-203	14
Total	38

QOW – every other week

Participants in 190-201 who completed 48 weeks of treatment at 300 mg QOW could enroll in 190-202 for additional treatment.

Table SIII.2: Cumulative Participant Exposure by Duration

	30 mg		100 mg		200 mg		300 mg [a]	
Duration of Exposure	**Persons**	**Person-Time (Months)**	**Persons**	**Person-Time (Months)**	**Persons**	**Person-Time (Months)**	**Persons**	**Person-Time (Months)**
Up to 24 Weeks	3	4.35	6	5.37	5	7.98	1	0.03
48 Weeks and Above	0	0	0	0	0	0	37	1890.08

6.9*6*7/I [a] Table reflects combined participant exposure from clinical trials 190-201/202 and 190-203.

Table SIII.3: Cumulative Participant Exposure By Age Group and Sex

Age Group (years) at Screening	**Male[a]**	**Female[a]**
≤ 5 years	13	21
> 5 years	2	2
Total	15	23

[a] Table reflects combined participant exposure from clinical trials 190-201/202 and 190-203.

Table SIII.4: Cumulative Participant Exposure By Dose

Dose of exposure	**Persons**	**Person-time (months)**
30 mg	3	4.35
100 mg	6	5.37
200 mg	5	7.98
300 mg	38[a]	1890.11[a]

[a] Table reflects combined participant exposure from clinical trials 190-201/202 and 190-203.

Table SIII.5: By Ethnic or Racial Origin

Race	Persons
Asian	1 (3%)
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
White	37 (97%)
Other	0
Ethnicity	**Persons**
Hispanic or Latino	3 (8%)
Not Hispanic or Latino	35 (92%)

Module SIV: Populations not studied in clinical trials

SIV.1: Exclusion criteria in pivotal clinical studies within the development programme

Participant has contraindications for neurosurgery (eg, severe respiratory impairment, clotting abnormalities)

- Reason for exclusion: Participants who cannot undergo neurosurgery will not be able to have the required implantation of the ICV access device necessary for delivery of BMN 190.
- Is it considered to be included as missing information: No.
- Rationale: Neurosurgery will be required for Brineura administration in the post-marketing setting; participants who are not suitable for neurosurgery will be contraindicated from receiving Brineura treatment.

Participant age 16 years or older

- Reason for exclusion: Patients with CLN2 disease who reach age 16 are rare. Reaching this age while still having mild CLN2 disease would not be representative of the typical CLN2 disease population and thus might influence the study results.
- Is it considered to be included as missing information: Yes (use in patients above 8 years of age; use in patients with advanced CLN2 disease).

Participant has another inherited neurologic disease or has another neurological illness that may have caused cognitive decline (eg, trauma, meningitis, hemorrhage)

- Reason for exclusion: The effects of other neurologic diseases and illnesses could affect the consistency and interpretation of study assessments.
- Is it considered to be included as missing information: No.
- Rationale: Treating physicians can determine whether the potential benefits of Brineura therapy outweigh the risks of concurrent illnesses/conditions on a case-by-case basis.

Participant requires ventilation support, except for noninvasive support at night

- Reason for exclusion: To ensure patient safety in use of a drug whose safety profile had not yet been established.
- Is it considered to be included as missing information: No.
- Rationale: Treating physicians can determine whether the potential benefits of Brineura therapy outweigh the risks of life-support device complications on a case-by-case basis.

Participant has received stem cell, gene therapy, or other ERT for CLN2 disease, or has received any investigational medication within 30 days before the start of BMN 190 treatment

- Reason for exclusion: Use of other therapies or investigational products could affect the consistency and interpretation of study assessments.
- Is it considered to be included as missing information: No.
- Rationale: Treating physicians can determine whether the potential benefits of Brineura therapy outweigh the risks of concurrent therapies on a case-by-case basis.

Participant has generalized motor status epilepticus within 4 weeks before the first dose (on both EEG and clinical examination)

- Reason for exclusion: The effects of other neurologic diseases and illnesses could affect the consistency and interpretation of study assessments.
- Is it considered to be included as missing information: No.
- Rationale: Treating physicians can determine whether the potential benefits of Brineura therapy outweigh the risks of disease complications on a case-by-case basis.

Participant is prone to complications from ICV drug administration, including participants with hydrocephalus or ventriculo-peritoneal shunts.

- Reason for exclusion: ICV access device implantation is required, and complications from ICV access device placement could confound findings and jeopardize participant safety.
- Is it considered to be included as missing information: No.
- Rationale: Treating physicians can determine whether the potential benefits of Brineura therapy outweigh the risks of ICV access device complications on a case-by-case basis.

Participant has a known hypersensitivity to cerliponase alfa or any of its components

- Reason for exclusion: The safety profile of cerliponase alfa had not yet been established.
- Is it considered to be included as missing information: No.
- Rationale: Cases of hypersensitivity occurred in clinical studies. Events were self-resolving or readily controlled with symptomatic treatment and/or infusion modification. The efficacy benefit of Brineura treatment outweighs the risk of severe hypersensitivity reactions.

Participant is pregnant

- Reason for exclusion: The safety profile of cerliponase alfa had not yet been established.
- Is it considered to be included as missing information: Yes.

SIV.2: Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3: Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

Special Populations	Persons	Person-years
Pregnant women	0	0
Lactating women	0	0
Renal impairment	1	5.5
Hepatic impairment	0	0
Cardiac impairment	2	11.3
Immunocompromised	3	14.1
Sub populations by genetic variant of *tpp1*		
• Two common alleles	16	67.3
• One common and one uncommon allele	13	52.6
• Two uncommon alleles	9	39.4

Renal impairment is defined as medical history terms that map to the Acute Renal Failure SMQ, Chronic Kidney Disease SMQ, Proteinuria SMQ, Renovascular Disorders SMQ, or Tubulointerstitial Diseases SMQ.

Cardiac impairment is defined as medical history terms that map to the Cardiac Arrhythmias SMQ, Cardiac Failure SMQ, Cardiomyopathy SMQ, Ischaemic Heart Disease SMQ, or Torsade de Pointes/QT Prolongation SMQ.

Hepatic impairment is defined as medical history terms that map to the Biliary Disorders SMQ or Hepatic Disorders SMQ.

Immunocompromise is defined as medical history terms that map to the Agranulocytosis SMQ or Haematopoietic Cytopenias SMQ.

Module SV: Post-authorisation experience

Brineura was approved for marketing in the United States on 27 April 2017 and in the European Union on 30 May 2017.

SV.1: Post-authorisation exposure

Table SV.1: Estimated Marketed Exposure Data

PBRER#	PBRER Reporting Period	Number of Cartons Sold / Distributed	Global Marketed Exposure Data (Patients Estimated)	
			Total # of Patients	% Change from Prior Period
1	27 April 2017 to 26 October 2017	299	42	N/A
2	27 October 2017 to 26 April 2018	590	70	66.7
3	27 April 2018 to 26 October 2018	844	95	35.7
4	27 October 2018 to 26 April 2019	1122	113	18.9
5	27 April 2019 to 26 October 2019	1624	152	34.5
6	27 October 2019 to 26 April 2020	2554	204	34.2
6a	27 April 2020 to 26 October 2020	2733	230	12.7
7	27 April 2020 to 26 April 2021	5925	260	13.0
8	27 April 2021 to 26 April 2022	6770	295	12.6

* Data extracted 03 May 2022.

Note: Due to General Data Protection Regulations (GDPR), patient numbers were calculated based on quantity shipped and compliance rate (eg, a patient with 100% compliance uses the equivalent of 1 vial per week [two vials every two weeks]).

SV1.1: Method used to calculate exposure

BioMarin International Ltd. tracks how many patients are receiving Brineura therapy and the source of the drug they received – commercial use, free drug use, or clinical trial use. Global patient exposure to Brineura were calculated based on quantity of drug shipped and compliance rate (eg, a patient with 100% compliance uses the equivalent of 1 vial per week [two vials every two weeks]). Participants who are enrolled in clinical trials but who transition to commercial drug once it becomes available are also tracked.

SV2.2: Exposure

Post-marketing exposure information by age group and gender is not available. All patients receiving Brineura in the post-marketing setting have done so by ICV access device for the indication of CLN2 disease.

Table SV.2: Post-authorization exposure for CLN2 disease

Region	Total Cumulative Exposure
NA	78
EMEA	172
APAC	10
LatAm	35
Total # of Patients	295

APAC = Asia-Pacific; EMEA = Europe, Middle East, and Africa; LatAm = Latin America; NA = North America

Note: Data extracted 03 May 2022.

Note: Due to patient privacy restrictions, sex and age group data were unavailable.

Note: The number of patients represents patients on therapy.

Note: Due to General Data Protection Regulations (GDPR), patient numbers were calculated based on quantity shipped and compliance rate (eg, a patient with 100% compliance uses the equivalent of 1 vial per week [two vials every two weeks]).

Module SVI: Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Brineura has no known potential for misuse for illegal purposes.

Module SVII: Identified and potential risks

Table SVII.1: Identification of safety concerns in the initial RMP submission

Summary of safety concerns from the initial RMP (Version 1.4, 24 April 2017)	
Important identified risks	• Hypersensitivity Reactions • Device Issues: device infection/blockage/dislocation/degradation • Convulsion related adverse drug reactions
Important potential risks	• Immunogenicity • Cardiac events/bradycardia • Hydrocephalus • Meningitis
Missing information	• Long Term Safety and Tolerability • Use in Pregnancy and During Lactation • Use in patients below 2 years of age • Use in patients above 8 years of age • Use in patients with advanced CLN2 disease

VII.1.1: Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

These events listed below are either common conditions known to occur in the age group being treated, known risks of the underlying disorder, or require routine management and/or no additional risk minimization measures. They do not meet the criteria for categorizing them as important safety concerns as per guidelines.

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Upper respiratory tract infection
- Conjunctivitis
- Irritability
- Headache
- Abdominal pain
- Oral mucosal blistering
- Tongue blistering
- Gastrointestinal disorder
- Feeling jittery
- Pain

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- None

Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the SmPC are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised):

- CSF Pleocytosis
- Rash
- Urticaria
- Vomiting
- Pyrexia
- ECG abnormalities
- Needle issue

Known risks that do not impact the risk-benefit profile:

- CSF protein increased/decreased
- Dropped head syndrome

Other reasons for considering the risks not important:

- Not applicable

SVII.1.2: Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: Hypersensitivity Reactions (Including Anaphylactic Reactions)

Risk-benefit impact: Exposure to cerliponase alfa, as with any exposure to a protein based medicinal product, may cause the body's immune system to produce antibodies or other inflammatory response to exposure. Pre-treatment with antihistamines with or without antipyretics approximately 30-60 minutes prior to the start of the cerliponase alfa infusion, to minimise the potential occurrence of hypersensitivity reactions, is recommended. Anaphylactic reactions have been reported with Brineura. As a precautionary measure, appropriate medical support should be readily available when Brineura is administered. If anaphylactic reactions occur, immediately discontinue the infusion and initiate appropriate medical treatment. Observe patients closely during and after the infusion. If anaphylaxis occurs, caution should be exercised upon re-administration.

By implementation of the risk minimization measures as per the SmPC, and following the Dosing and Administration guide provided to healthcare providers (HCPs) the risk is manageable. Overall, the risk is not expected to outweigh the benefit in the patient population. The individual patient risk-benefit balance should be made by the treating physician on a case-by-case basis.

Important Identified Risk: Device Issues (Device Infection/Blockage/Dislocation)

Risk-benefit impact: Device related AEs were experienced by subjects receiving cerliponase alfa via an implanted ICV reservoir. Most events resolve either spontaneously or with minimal medical intervention. Neurosurgical evaluation with subsequent ICV access device removal and/or replacement may be required. By implementation of the risk minimization measures as per the SmPC, and following the Dosing and Administration guide provided to HCPs the risk is manageable.

Important Identified Risk: Convulsion-Related Adverse Drug Reactions

Risk-benefit impact: Convulsions are a common manifestation of CLN2 disease and are expected to occur in this population. In clinical studies, convulsion AEs ranging from mild to severe (NCI CTCAE grade 1-4) have been observed. Most events resolve either

spontaneously or with minimal medical intervention (anticonvulsant medications). By implementation of the risk minimization measures as per the SmPC the risk is manageable.

Important Potential Risk: Immunogenicity

Risk-benefit impact: Development of anti-drug antibodies is a common occurrence in ERT therapy. Exposure to cerliponase alfa may cause the body's immune system to produce antibodies, which interact with administered drug and can have a potential impact on safety or efficacy in treated patients. Anti-drug antibodies (ADA) to cerliponase alfa were detected in the serum and in the CSF of subjects in clinical studies. However, no correlation has been observed between immunogenicity study results and safety, pharmacokinetics (PK), or efficacy measures in the cerliponase alfa clinical studies.

Important Potential Risk: Cardiac Events/Bradycardia

Risk-benefit impact: Cardiac events were observed with cerliponase alfa. These included cardiac events such as bradycardia and vascular disorders such as hypotension. No correlation has been observed between cardiac events or bradycardia and safety or efficacy measures in the cerliponase alfa clinical studies.

Important Potential Risk: Hydrocephalus

Risk-benefit impact: Hydrocephalus is a known complication from ICV medicinal product administration. No events of hydrocephalus were reported during clinical studies with cerliponase alfa.

Important Potential Risk: Meningitis

Risk-benefit impact: Meningitis is known complication with the use of ICV access devices. Intracerebroventricular access device-related infections, including sub-clinical infections and meningitis, have been observed in patients treated with Brineura. Meningitis may present with the following symptoms: fever, headache, neck stiffness, light sensitivity, nausea, vomiting, and change in mental status. CSF samples should routinely be sent for testing to detect subclinical device infections. In clinical studies, antibiotics were administered, the ICV access device was replaced, and Brineura treatment was continued. By implementation of the risk minimization measures as per the SmPC, and following the Dosing and Administration guide provided to the HCPs the risk is manageable.

Missing Information: Long Term Safety and Tolerability

Risk-benefit impact: Due to the low prevalence of this genetic disease in the general population, the overall clinical trial sample is small and does not allow for an extensive assessment of rare adverse events. Safety and tolerability of the drug over long term usage needs to be determined.

Missing Information: Use in Pregnancy and During Lactation

Risk-benefit impact: Due to the low prevalence of this genetic disease in the general population, the overall clinical trial sample is small and does not allow for an extensive assessment of rare adverse events. Safety and tolerability of the drug during pregnancy and lactation usage needs to be determined.

Missing Information: Use in Patients Below 2 Years of Age

Risk-benefit impact: Due to the low prevalence of this genetic disease in the general population, the overall clinical trial sample is small and does not allow for an extensive assessment of rare adverse events. Safety and tolerability of the drug in children under 2 years of age needs to be determined.

Missing Information: Use in Patients Above 8 Years of Age

Risk-benefit impact: Due to the low prevalence of this genetic disease in the general population, the overall clinical trial sample is small and does not allow for an extensive assessment of rare adverse events. Safety and tolerability of the drug in patients over 8 years of age needs to be determined.

Missing Information: Use in Patients with Advanced CLN2 Disease

Risk-benefit impact: Due to the low prevalence of this genetic disease in the general population, the overall clinical trial sample is small and does not allow for an extensive assessment of rare adverse events. Safety and tolerability of the drug in patients with advanced disease needs to be determined.

SVII.2: New safety concerns and reclassification with a submission of an updated RMP

Removal of Immunogenicity as an Important Potential Risk:

Immunogenicity that was previously classified as an important potential risk has been removed from the list of safety concerns.

Rationale for removal from the list of safety concerns:

Immunogenicity was evaluated in 190-201/202 and 190-203 studies. Immunogenicity testing was performed using validated immunogenicity assays on serum and CSF samples. Routine immunogenicity tests included total antibody (TAb) in the serum and CSF and neutralizing antibody (NAb) in the CSF. NAb testing was not performed if the CSF TAb was negative.

190-202 Key Immunogenicity Findings: The immunogenicity strategy for the study included characterizing the anti-drug antibody (ADA) response and assessing the impact of ADA on safety, exposure and efficacy. Anti-drug antibodies were detected in the serum in 79% (19/24) and in the cerebrospinal fluid (CSF) of 42% (10/24) participants. Serum TAb titers were either sustained (12/19, 63%) declined (5/19, 26%), or reverted to

undetectable (2/19, 11%) in participants that developed antibodies by end of study. There was no association found between serum ADA titer and incidence or severity of hypersensitivity AEs (HAEs). There was no drug-specific IgE positivity detected in participants who experienced Grade 3 hypersensitivity AEs. There was no association found between serum or CSF TAb titers and treatment outcome. The development of an ADA response to cerliponase alfa in the serum or CSF was not correlated with or predictive of any clinical signals impacting either safety or efficacy outcomes.

190-203 Key Immunogenicity Findings: The immunogenicity strategy for the study included characterizing the ADA response and assessing the impact of ADA on safety, exposure and efficacy. Incidence of ADA in serum was 100% (14/14) of participants; earliest time to onset was week 13 after treatment initiation. 36% (5/14) of participants had declining or transient TAb responses while 64% (9/14) of participants had sustained TAb titers. No drug-specific IgE positivity was detected in the 2 participants that experienced Grade 3 HAE or anaphylaxis. Participants with higher mean serum TAb titers reported hypersensitivity AEs of similar incidence and severity as participants with lower mean serum TAb titers. Additionally, participants not reporting hypersensitivity AEs also had detectable serum TAb titers. Overall, the immunogenicity profile of cerliponase alfa in this younger pediatric population was consistent with and supportive of the positive benefit-risk profile assessed in the older pediatric population in 190-201/202.

Current data indicate that the utility of ADA results in influencing clinical decision-making with regards to patient treatment options is minimal. The assays were only available as part of the BMN 190 clinical development programme and are not available in the commercial treatment setting.

The risk for immunogenicity is noted in the EU SmPC in Section 4.8 “Undesirable effects”. No updates to the SmPC are currently warranted.

SVII.3: Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

SVII.3.1: Presentation of important identified risks and important potential risks

Important Identified Risk: Hypersensitivity Reactions (Including Anaphylactic Reactions)

MedDRA terms: Standardized MedDRA queries (SMQ): Broad algorithmic Anaphylactic reaction and broad Hypersensitivity

Potential mechanism: As with any exposure to a protein based medicinal product, severe allergic type reactions are possible. Exposure to cerliponase alfa may cause the body's immune system to produce antibodies or other inflammatory response to cerliponase alfa.

Evidence source(s) and strength of evidence: Hypersensitivity reactions are not unanticipated with any exposure to a protein-based medicinal product. Hypersensitivity reactions have been reported in patients exposed to cerliponase alfa in clinical studies (190-201/202, and 190-203). Most of the events were observed during or within 24 hours after completion of infusion suggesting that these reactions are likely related to the cerliponase alfa treatment. Cumulatively, there have been 3 reports of anaphylactic reactions. One report was received from a clinical trial and 2 reports were received from post-marketing sources.

Characterization of the risk: Hypersensitivity AEs (HAEs) were expected to occur with cerliponase alfa, as with any biologic agent. Potential hypersensitivity AEs were identified by utilizing the broad algorithmic Anaphylactic reaction SMQ and the broad Hypersensitivity SMQ.

In 190-201/202 studies, a total of 56 hypersensitivity events were reported in 18 participants (75%). The hypersensitivity events reported more than once were hypersensitivity (16 events in 10 participants), rash (9 events in 3 participants), conjunctivitis (7 events in 6 participants), dermatitis contact (6 events in 5 participants), seasonal allergy (4 events in 3 participants), choking (2 events in 2 participants) and urticaria (2 events in 2 participants). No other hypersensitivity event was reported more than once. Out of 56 hypersensitivity events, 22 hypersensitivity events were assessed as related to cerliponase alfa by investigator. Related hypersensitivity events include 16 events of hypersensitivity PTs in 10 participants, 3 events of rash in 2 participants, 1 event of conjunctivitis in 1 participant, 1 event of face oedema in 1 participant, and 1 event of urticaria in 1 participant. Most hypersensitivity events were mild to moderate in severity (CTCAE Grade 1 or 2) in 190-201/202 studies. There were no events of anaphylaxis or anaphylactoid reactions in studies 190-201/202.

In 190-203 study, a total of 36 hypersensitivity events were reported in 10 (71.4 %) participants. Hypersensitivity events reported in more than 1 participant included hypersensitivity (20 events in 4 participants), rash (4 events in 3 participants), and stomatitis (2 events in 2 participants). Cerliponase alfa was interrupted in response to 1 event of Grade 3 anaphylactic reaction. Upon further medical review, it was identified that out of 36 events, 21 events which were assessed as related to cerliponase alfa are the hypersensitivity reactions to study drug. The other not related hypersensitivity events had alternative etiological factors. Out of these 21 hypersensitivity reactions, 20 events were hypersensitivity (PT) and 1 event was anaphylactic reaction. Two participants experienced a Grade 3 AE, including 1 event of hypersensitivity and 1 event of anaphylactic reaction. Hypersensitivity reactions were reported in 5 of 8 (63%)

participants < 3 years of age as compared with no incidences in participants ≥ 3 years of age. Out of 21 related hypersensitivity events, AE onset age for 16 events was less than 3 years and AE onset age for 5 events was more than 3 years. The AE onset age of both the Grade 3 events was less than 3 years (AE onset age of Grade 3 hypersensitivity event was 2.6 years and AE onset age of Grade 3 anaphylactic reaction was 1.1 years).

Cumulatively out of 38 participants in clinical trials, hypersensitivity reactions were reported in 5 of 8 (63%) participants less than 3 years of age compared with 14 of 30 (47%) in participants ≥3 years of age.

Hypersensitivity reactions, particularly in patients less than 3 years of age in whom Brineura treatment is initiated, will be further evaluated in the Post-Authorization Safety Study (PASS) (190-504: CLN2 Post-Approval Observational Study).

For reports of hypersensitivity, the most commonly reported symptoms were pyrexia, vomiting, pleocytosis, or irritability, which are not consistent with classic immune mediated hypersensitivity and are not listed in the broad hypersensitivity SMQ. These events were observed during or within 24 hours after completion of the Brineura infusion and did not interfere with treatment.

A query for HAEs (consisting of the broad MedDRA hypersensitivity SMQ and broad algorithmic anaphylactic reactions SMQ) was run to identify HAEs received in the post-marketing setting. Based on this search, cumulatively as of 26 April 2022, 48 reports of HAEs (including 65 total events) have been received from post-marketing sources, including 20 serious HAEs.

Cumulatively, there have been 3 reports of anaphylactic reactions. One report was received from a clinical trial and 2 reports were received from post-marketing sources.

Risk factors and risk groups: None identified

Preventability:

Pre-treatment with antihistamines with or without antipyretics approximately 30- 60 minutes prior to the start of the cerliponase alfa infusion, to minimise the potential occurrence of hypersensitivity reactions, is recommended.

In case of a mild or moderate hypersensitivity reaction, treatment with antihistamines and paracetamol and/or a reduction in the infusion rate to half the rate at which the reaction occurred should be considered.

In case of a single severe hypersensitivity reaction, the infusion should be stopped until the symptoms are resolved and treatment with antihistamines and acetaminophen should be considered. The infusion can be restarted with a reduction of the infusion rate to 50%–25% of the rate at which the reaction occurred.

In case of a recurrent moderate hypersensitivity reaction or re-challenge after a single severe hypersensitivity reaction, pre-treatment should be considered (antihistamines and acetaminophen and/or corticosteroids) and a reduction of the infusion rate to 50%–25% of the rate at which the previous reaction occurred.

Impact on the risk-benefit balance of the product: Exposure to cerliponase alfa, as with any exposure to a protein based medicinal product, may cause body's immune system to produce antibodies or other inflammatory response to exposure. Pre-treatment with antihistamines with or without antipyretics approximately 30-60 minutes prior to the start of the cerliponase alfa infusion, to minimise the potential occurrence of hypersensitivity reactions, is recommended. By implementation of the risk minimization measures as per the SmPC and following the Dosing and Administration guide provided to HCPs the risk is manageable. Overall, the risk is not expected to outweigh the benefit in the patient population. The individual patient risk-benefit balance should be made by the treating physician on a case-by-case basis.

Public health impact: Very low.

Important Identified Risk: Device Issues (Device Infection/Blockage/Dislocation/ Degradation)

MedDRA terms: Any PT within the HLGT of Device Issues

Potential mechanism: As with any implanted medical device, failure of the device, infection due to translocation of pathogen, occlusion or mispositioning, may occur.

Evidence source(s) and strength of evidence: Cerliponase alfa should be administered intraventricularly via an implanted ICV reservoir. As with any neurosurgical device, issues with the ICV device such as infection, blockage, and dislocation etc. are known to occur. Device issues, including infection, have been observed in patients exposed to cerliponase alfa in clinical studies.

Characterization of the risk: Device-related AEs were experienced by participants receiving cerliponase alfa via an implanted ICV reservoir.

In 190-201/202 studies, 20 participants (83%) experienced a total of 72 AEs assessed as device related. Device-related AEs that occurred in more than 1 participant were device-related infection (13 events in 8 participants), device end of service (12 events in 12 participants), device leakage (9 events in 3 participants), device malfunction (8 events in 3 participants), needle issue (6 events in 5 participants), pleocytosis (4 events in 4 participants), device difficult to use (4 events in 2 participants), and device deployment issue (2 events in 2 participants). No other device-related AE was reported more than once in 190-201/202. Of the 72 device-related AEs, twelve device-related AEs were reported with CTCAE grade 3 in 6 participants. No event of device-related AEs with Grade 4 severity was reported in 190-201/202. A total of 14 device-related AEs in 7

participants led to ICV device replacement, including device related infection (8 events in 6 participants), device leakage (2 events in 2 participants), device deployment issue (2 events in 2 participants), device malfunction (1 event in 1 participant) and Propionibacterium infection (1 event in 1 participant). All the ICV devices were successfully replaced without complication and without discontinuation of study drug.

In 190-203 study, 5 participants experienced 8 device-related AEs. The most common device-related event was device leakage (4 events in 3 participants). In addition, there was 1 event each of propionibacterium test positive, device breakage, headache, and medical device site irritation. Three participants experienced 3 SAEs including one Grade 3 SAE of Propionibacterium test positive, one Grade 2 SAE of device leakage (described as leak of CSF from ICV device), and one Grade 2 SAE of medical device site irritation. There was no substantial difference in the incidence and severity of device-related AEs between age subgroups (< 2, < 3, ≥ 3 years). There were no ICV malfunctions or AEs leading to the removal and return of an ICV device.

From post-marketing sources, cumulatively as of 26 April 2022, 66 events have been reported from 62 reports involving device issues from post-marketing sources (device leakage [23 events], needle issue [10 events], device occlusion [9 events], device issue [7 events], device malfunction [6 events], device breakage [3 events], device dislocation [3 events], device end of service [2 events], device infusion issue [1 event], device failure [1 event], and device kink [1 event]). In addition, 74 events of device-related infections have been reported from the post-marketing setting.

Material degradation of the ICV access device reservoir occurs after long periods of use according to preliminary results of benchtop testing and as observed in clinical trials with approximately 4 years of use. In two clinical cases, the ICV access devices did not show signs of failure at the time of infusion; however, after removal, material degradation of the devices was apparent and consistent with data from benchtop testing of ICV access devices. The access devices were replaced and patients resumed treatment with Brineura. Access device replacement should be considered prior to 4 years of regular administration of Brineura, however it must always be ensured, that the ICV access device is used in accordance with the provisions of the respective medical device manufacturer.

Risk factors and risk groups: None identified

Preventability: Cerliponase alfa must be administered using aseptic technique to reduce the risk of infection. Healthcare professionals should inspect the scalp for skin integrity to ensure the ICV access device is not compromised prior to each infusion. A patency check should be performed to detect ICV access device leakage and/or failure prior to initiation of Brineura.

Impact on the risk-benefit balance of the product: Device related AEs were experienced by participants receiving cerliponase alfa via an implanted ICV reservoir. Most AEs

resolve either spontaneously or with minimal medical intervention. Neurosurgical evaluation with subsequent ICV access device removal and/or replacement may be required. By implementation of the risk minimization measures as per the SmPC and following the Dosing and Administration guide provided to the HCPs the risk is manageable.

Public health impact: Very low

Important Identified Risk: Convulsion Related Adverse Drug Reactions

MedDRA terms: Standardized MedDRA queries (SMQ): Convulsions; searches for events of status epilepticus include the MedDRA PTs of status epilepticus and petit mal epilepsy

Potential mechanism: Unknown

Evidence source(s) and strength of evidence: Convulsions are a common manifestation of CLN2 disease and are expected to occur in this population. Convulsions were reported in 31 (81.5 %) of 38 patients exposed to cerliponase alfa in clinical studies (190-201/202 and 190-203). The majority (>90%) of these events were mild to moderate, and 4% were considered related to cerliponase alfa.

Characterization of the risk: A total of 31 (81.5 %) of 38 participants who received cerliponase alfa experienced an AE that mapped to the Convulsions SMQ in clinical studies (190-201/202 and 190-203).

In 190-201/202 studies, 23 (96%) participants experienced 693 AEs that map to the Convulsions Standardized MedDRA Query. Twenty participants (83%) had convulsion AEs that were Grade 1 or 2 in severity, and 12 participants experienced 27 convulsion events considered related to study drug. One participant (4%) experienced a Grade 3 event of seizure and status epilepticus, and 1 participant (4%) experienced a Grade 4 event of status epilepticus. Six participants (25%) experienced 7 convulsion AEs that occurred after ICV implantation but before first dose of cerliponase alfa. Sixteen participants (67%) experienced 90 convulsion AEs that occurred within 24 hours of the start of cerliponase alfa infusion.

In 190-203 study, one participant experienced a single Grade 3 SAE of status epilepticus assessed by the investigator as not related to cerliponase alfa. No change in cerliponase alfa dosing was made in response to this event. Eight participants (57.1%) reported 74 AEs that mapped to the Convulsions Standardized MedDRA Query. The most common convulsion AEs included partial seizures (28 events in 3 participants), generalized tonic-clonic seizure (18 events in 6 participants), and seizure (8 events in 3 participants). All convulsion AEs were Grade 1 or 2 in severity, with the exception of the Grade 3 event of status epilepticus. All convulsion events were assessed by the investigator as not related to cerliponase alfa. There was no substantial difference in the incidence and severity of

convulsion AEs between age subgroups (< 2, < 3, ≥ 3 years). Most convulsion AEs occurred in symptomatic participants [motor-language (ML) < 6 points at baseline]; 5 of 7 symptomatic participants experienced 64 [87%] of the total convulsion AEs.

Most AEs resolve either spontaneously or with minimal medical intervention (anticonvulsant medications). Given that seizures are a common manifestation in patients with CLN2 disease, the overall number of events is not surprising. Overall, few of the convulsion AEs were considered related to study drug or occurred within 24 hours of a dose, suggesting no worsening effect of BMN 190 via ICV delivery on this common disease manifestation.

From post-marketing sources, cumulatively as of 26 April 2022, 125 convulsion-related events (in 116 reports) have been reported (94 events of seizure, 7 events of status epilepticus, 5 events of generalised tonic-clonic seizure, 4 events of partial seizures, 4 events of epilepsy, 2 events of myoclonic epilepsy, 2 events of petit mal epilepsy, and 1 event each of tonic posturing, automatism epileptic, gelastic seizure, clonic convulsion, febrile convulsion, déjà vu, and infantile spasms).

Risk factors and risk groups: None identified

Preventability: Clinical monitoring and medical intervention as needed

Impact on the risk-benefit balance of the product: Convulsions are a common manifestation of CLN2 disease and are expected to occur in this population. In clinical studies, convulsion AEs ranging from mild to severe (NCI CTCAE grade 1-4) have been observed. Most events resolve either spontaneously or with minimal medical intervention (anticonvulsant medications). By implementation of the risk minimization measures as per the SmPC the risk is manageable.

Public health impact: Very low

Important Identified Risk: Meningitis

MedDRA terms:

• Central Nervous System Infection • Meningitis • Meningitis aseptic • Meningitis aspergillus • Meningitis bacterial • Meningitis borrelia • Meningitis candida • Meningitis chemical • Meningitis coccidioides • Meningitis coxsackie viral	• Meningitis histoplasma • Meningitis leptospiral • Meningitis listeria • Meningitis meningococcal • Meningitis mumps • Meningitis neonatal • Meningitis noninfective • Meningitis pneumococcal • Meningitis salmonella • Meningitis staphylococcal

• Meningitis cronobacter • Meningitis cryptococcal • Meningitis echo viral • Meningitis enterococcal • Meningitis enteroviral • Meningitis eosinophilic • Meningitis exserohilum • Meningitis fungal • Meningitis gonococcal • Meningitis haemophilus • Meningitis herpes	• Meningitis streptococcal • Meningitis toxoplasmal • Meningitis trypanosomal • Meningitis tuberculous • Meningitis viral • Herpes zoster meningitis • Herpes simplex meningitis • Pachymeningitis • Propionibacterium infection • Pseudomonas aeruginosa meningitis

Potential mechanism: Unknown

Evidence source(s) and strength of evidence: Cerliponase alfa should be administered intraventricularly via an implanted ICV reservoir. As with any neurosurgical device, there is a potential for inflammation of the meninges due to infectious agents. ICV access device-related infections, including sub-clinical infections and meningitis, have been observed in patients treated with Brineura. Meningitis may present with the following symptoms: fever, headache, neck stiffness, light sensitivity, nausea, vomiting, and change in mental status. CSF samples should routinely be sent for testing to detect subclinical device infections. In clinical studies, antibiotics were administered, the ICV access device was replaced, and Brineura treatment was continued.

Characterization of the risk: Meningitis may range from mild and asymptomatic to severe; antimicrobial therapy and neurosurgical evaluation with subsequent ICV access device removal and/or replacement may be required. No events of meningitis were reported during clinical trials with Brineura. A query was performed using a pre-specified list of MedDRA preferred terms to identify reports from post marketing sources (refer to MedDRA terms described above). Cumulatively as of 26 April 2022, 34 events of meningitis have been reported in the post-marketing setting (16 events of central nervous system infection, 8 events of meningitis, 4 events of Propionibacterium infection, 3 events of meningitis bacterial, 2 events of meningitis eosinophilic, and 1 event of meningitis staphylococcal).

Risk factors and risk groups: None identified

Preventability: Clinical monitoring and medical intervention as indicated. Neurosurgical evaluation and intervention may be required. Cerliponase alfa must be administered using aseptic technique to reduce the risk of infection. Healthcare professionals should inspect the scalp for skin integrity to ensure the ICV access device is not compromised prior to

each infusion. A patency check should be performed to detect ICV access device leakage and /or failure prior to initiation of Cerliponase alfa.

Impact on the risk-benefit balance of the product: Meningitis is a known complication with the use of ICV access devices. ICV access device-related infections, including sub-clinical infections and meningitis, have been observed in patients treated with Brineura. In clinical studies, antibiotics were administered, the ICV access device was replaced, and Brineura treatment was continued. By implementation of the risk minimization measures as per the SmPC and following the Dosing and Administration guide provided to HCPs, the risk is manageable.

Public health impact: Very low

Important Potential Risk: Cardiac Events/Bradycardia

MedDRA terms: Any PT within the SOC of vascular disorder, SOC of cardiac disorder, HLT of ECG investigations or HLGT of cardiac and vascular investigations

Potential mechanism: Unknown

Evidence source(s) and strength of evidence: Cardiac events were observed with cerliponase alfa during clinical studies (190-201/202 and 190-203). These included cardiac events such as bradycardia and vascular disorders such as hypotension. No correlation has been observed between cardiac events or bradycardia and safety or efficacy measures in the cerliponase alfa clinical studies. Hence these events were considered as a potential risk for cerliponase alfa.

Characterization of the risk:

In 190-201/202 studies, seven participants (29%) experienced 15 cardiovascular and ECG AEs. All events were non-serious and Grade 1 or 2 in severity and did not require changes in cerliponase alfa dosing. The most common events were bradycardia (4 events in 2 participants), hypotension (3 events in 3 participants), and hematoma (2 events in 2 participants). Additional single events of cardiovascular disorder, sinus bradycardia, tachycardia, blood pressure diastolic decreased, and cardiac murmur were reported in 1 participant each. There was one ECG abnormality (T wave inversion) which was Grade 1 in severity and assessed as not related to cerliponase alfa.

In 190-203 study, three participants experienced 4 cardiovascular AEs, including hematoma in 1 participant, atrioventricular block in 1 participant, and hypertension and electrocardiogram abnormal in 1 participant. All events were assessed by the investigator as non-serious and Grade 1 in severity. The event of atrioventricular block was later upgraded by BioMarin to serious based on medical significance and conservatively assessed as possibly related to BMN 190 due to the absence of alternative aetiological factors and the strong temporal relationship. Additionally, a single event of Grade 1

congenital cardiac malformation was identified; this event was assessed as non-serious and not related to study drug or ICV device.

In the post-marketing setting, cumulatively as of 26 April 2022, 52 events from 39 reports were identified. Further medical review revealed that 32 events were non-cardiac events secondary to other concurrent non-cardiac events. Twenty (20) events from 19 reports were found to be cardiac events (4 events of tachycardia, 3 events of bradycardia, 2 events of cardiac arrest, 2 events of angina pectoris, 2 events of hypertension, 2 events of heart rate increased, and 1 each event of arteriosclerosis, ventricular enlargement, cardiopulmonary failure, syncope, and ventricular hypertrophy).

Risk factors and risk groups: None identified

Preventability: Clinical monitoring and medical intervention as indicated.

Impact on the risk-benefit balance of the product: Cardiac events were observed with cerliponase alfa. These included cardiac events such as bradycardia and vascular disorders such as hypotension. No correlation has been observed between cardiac events or bradycardia and safety or efficacy measures in the cerliponase alfa clinical studies.

Public health impact: Very low

Important Potential Risk: Hydrocephalus

MedDRA terms: Preferred Terms: Congenital hydrocephalus and Hydrocephalus

Potential mechanism: Unknown

Evidence source(s) and strength of evidence: Cerliponase alfa should be administered intraventricularly via an implanted ICV reservoir. As with any neurosurgical device, there is a potential for development of hydrocephalus (communicating or non-communicating) due to the ICV device. No events of hydrocephalus were reported in clinical studies (190-201/202 and 190-203).

Characterization of the risk: No events of hydrocephalus have been reported during clinical trials with Brineura. Cumulatively as of 26 April 2022, 2 events of hydrocephalus have been reported in the post-marketing setting.

Risk factors and risk groups: None identified

Preventability: Clinical monitoring and medical intervention as indicated. Neurosurgical evaluation and intervention may be required.

Impact on the risk-benefit balance of the product: Hydrocephalus is a known complication from ICV medicinal product administration. No events of hydrocephalus have been reported during clinical studies with cerliponase alfa.

Public health impact: Very low

SVII.3.2: Presentation of missing information

Missing Information: Long Term Safety and Tolerability

MedDRA terms: None

Evidence Source: The safety profile is not expected to be different than in the target population.

Anticipated risk/consequence of the missing information: A lack of long-term safety and tolerability data could affect the ability to detect adverse reactions which are rare, which are due to prolonged exposure, which are due to cumulative effects of cerliponase alfa use, or which have a long latency period. Data will be collected from long-term use in, post-marketing reports, and the Post-Authorization Safety Study (PASS) (190-504: CLN2 Post-Approval Observational Study).

Missing Information: Use in Pregnancy and During Lactation

MedDRA terms: Congenital, familial and genetic disorders (SMQ), Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ), Functional lactation disorders (SMQ), Neonatal exposures via breast milk (SMQ), Foetal disorders (SMQ), Neonatal disorders (SMQ), Termination of pregnancy and risk of abortion (SMQ), Normal pregnancy conditions and outcomes (SMQ)

Evidence Source: Due to the predominant pediatric presentation of the disease, the safety profile in pregnant and/or lactating patients is unknown.

Population in need of further characterization: There have been no patients who have received cerliponase alfa and have become pregnant or engaged in breastfeeding. Section 4.6 of the SmPC states that there are no data with cerliponase alfa use in pregnant women to inform on drug-associated risk. Animal reproduction studies have not been conducted using cerliponase alfa. It is not known whether cerliponase alfa can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Cerliponase alfa should be given to a pregnant woman only if clearly needed. Section 4.6 of the SmPC also states that there are no data on the presence of cerliponase alfa in human milk, the effects of cerliponase alfa on the breastfed child, or the effects of cerliponase alfa on milk production, and states that breastfeeding should be discontinued during treatment with Brineura. It is not known whether patients who are pregnant or breastfeeding would respond differently to cerliponase alfa therapy than other participants.

Missing Information: Use in Patients Below 2 Years of Age

MedDRA terms: None

Evidence Source: The safety profile is not expected to be different than in the target population.

Population in need of further characterization: In 190-203 study, 5 (35.7 %) of 14 participants exposed to study drug were below 2 years of age (baseline age). Safety and efficacy were evaluated for these 5 subjects in 190-203 study. Study 190-504 (Cerliponase Alfa Observational Study) is ongoing and the primary objective of this study is to evaluate the long-term safety of cerliponase alfa. MAH is expecting to receive more data for patients below 2 years of age from 190-504 study. The SmPC (Section 4.2) provides a recommended dosing strategy for patients under the age of 2, based on the age of the patient at the time of treatment.

Missing Information: Use in Patients Above 8 Years of Age

MedDRA terms: None

Evidence Source: The safety profile is not expected to be different than in the target population.

Population in need of further characterization: The SmPC (Section 4.2) states that there is limited data with cerliponase alfa use in patients older than 8 years of age. Safety data on patients in this age group is to be collected from post-marketing use and from the PASS (190-504: CLN2 Post-Approval Observational Study).

Missing Information: Use in Patients with Advanced CLN2 Disease

MedDRA terms: None

Evidence Source: The safety profile is not expected to be different than in the target population.

Population in need of further characterization: There are limited data in patients with advanced disease progression at treatment initiation (defined as a motor-language score of 0 on the CLN2 rating scale) who were included in clinical trials (stated in Section 4.4 of the SmPC). Safety data on patients with advanced CLN2 disease is to be collected from post-marketing use and from the PASS (190-504: CLN2 Post-Approval Observational Study).

Module SVIII: Summary of the safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity Reactions (Including Anaphylactic Reactions) Device Issues (Device Infection/Blockage/ Dislocation/Degradation) Convulsion-Related Adverse Drug Reactions Meningitis
Important potential risks	Cardiac Events/Bradycardia Hydrocephalus
Important missing information	Long Term Safety and Tolerability Use in Pregnancy and During Lactation Use in Patients Below 2 Years of Age Use in Patients Above 8 Years of Age Use in Patients with Advanced CLN2 Disease

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION STUDIES)

III.1: Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for Hypersensitivity Reactions (Including Anaphylactic Reactions):

A questionnaire will be used to collect information on the infusion-associated AEs. This form requests the HCP to provide more details on the relevant medical history, concomitant medications, drug exposure history of the patient, signs and symptoms of the infusion associated reaction by organ system, clinical course, vital signs, laboratory tests, treatment, and re-introduction information.

A copy of this form is provided in Annex 4.

Specific adverse reaction follow-up questionnaires for Device Issues (Device Infection/Blockage/Dislocation/Degradation):

A questionnaire will be used to collect information on device-related AEs. This form requests the HCP to provide more details on the actual device associated with the AE, including the type, manufacturer name and model, date of implantation and removal of the device, along with the details of the adverse reaction observed in the patient.

A copy of this form is provided in Annex 4.

Specific adverse reaction follow-up questionnaires for Use in Pregnancy and During Lactation:

A questionnaire will be used to collect information on pregnancy and lactation. This form requests the HCP to provide more details on pregnancy history, contraception use, date of last menstrual period, estimated/actual date of delivery, pregnancy complications, pregnancy outcome (including type of delivery, infant outcome, Apgar score, and other relevant details), and drug exposure prior to and/or during pregnancy.

A copy of this form is provided in Annex 4.

III.2: Additional pharmacovigilance activities

Study 190-504 (EU): Cerliponase Alfa Observational Study

Study short name and title: 190-504: Cerliponase Alfa Observational Study

Rationale and study objectives:

The primary objective of this non-interventional post-authorization safety study (PASS) study is to evaluate the long-term safety of cerliponase alfa in patients with neuronal ceroid lipofuscinosis Type 2 (CLN2 disease).

The secondary objectives of this study include the following:

- To further assess the occurrence of serious hypersensitivity reactions (including anaphylactic reactions), serious cardiovascular adverse events, and serious device-related complications
- To evaluate the effects of Grade III serious adverse events (SAEs) on patient performance on the CLN2 Clinical Rating Scale (Motor and Language domains)

Study design:

Investigators are encouraged to follow the Recommended Schedule of Events, which includes assessments to monitor the long-term safety of CLN2 patients who are currently being treated, or who plan to be treated with cerliponase alfa within 60 days of signing the ICF/PIAF. Data may be collected for all or some of the assessments dependent upon the individual's standard of care. Patients that permanently stop receiving cerliponase alfa will be withdrawn from the study 30 days after the last cerliponase alfa infusion.

Study population:

Patients who are currently being treated, or who plan to be treated with cerliponase alfa within 60 days of signing the ICF are eligible to participate in the study. Patients who permanently discontinue cerliponase alfa will no longer be eligible to participate and will be withdrawn from the study.

Milestones:

- Protocol submission: 21 June 2017

The original protocol was submitted and agreed with the EMA via a closing sequence on 21 June 2017. However, following internal discussions the protocol has been revised. Feedback was received by the PRAC on 19 June 2018 (EMEA-H-C-PSP-S-0063) with a request for further changes. BioMarin amended the protocol to address the PRAC specific concerns and submitted the revised protocol for PRAC assessment on 20 August 2018. PRAC feedback was received in October 2018 requesting to further justify the changes to the protocol. Although no further changes were made to the protocol, BioMarin has submitted responses to PRAC. The revised protocol was approved on 19 March 2019.Interim reports: To be provided annually to EMA

- Final report: 2030 (anticipated)

III.3: Summary Table of Additional Pharmacovigilance Activities

Table III.1: On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
190-504 (EU) (PASS) Cerliponase Alfa Observational Study (Study Status: Ongoing)	The primary objective of this study is to evaluate the long-term safety of cerliponase alfa in patients with neuronal ceroid lipofuscinosis Type 2 (CLN2 disease). The secondary objectives of this study include the following: • To further assess the occurrence of serious hypersensitivity reactions (including anaphylactic reactions), serious cardiovascular adverse events, and serious device-related complications • To evaluate the effects of Grade III serious adverse events (SAEs) on patient performance on the CLN2 Clinical Rating Scale (Motor and Language domains)	Additional data collected will help broaden knowledge of identified and potential risks of cerliponase alfa, as well as provide new information on long-term safety.	Original protocol submission	June 2017
			Revised protocol submission:	August 2018
			Revised protocol approval:	19 March 2019
			Interim Reports	Annually
			Final CSR (anticipated)	2030
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table IV.1: Planned and On-going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

PART V: RISK MINIMISATION MEASURES

Risk Minimisation Plan

V.1: Routine Risk Minimisation Measures

Table V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Hypersensitivity Reactions (Including Anaphylactic Reactions)	**Routine risk communication:** SmPC: Section 4.2, Section 4.4, Section 4.8 Package leaflet (PL): Section 2, Section 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation for pre-treatment of patients with antihistamines with or without antipyretics 30 to 60 minutes prior to the start of the infusion is included in SmPC Section 4.2. SmPC Section 4.2 states that if an infusion is interrupted due to a hypersensitivity reaction, it should be restarted at approximately one-half the initial infusion rate at which the hypersensitivity reaction occurred. Caution on the risk of anaphylaxis and possible symptoms of anaphylaxis are provided to the health care professionals in the Section 4.4 of SmPC and PL Section 2. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.
Device Issues (Device Infection / Blockage / Dislocation / Degradation)	**Routine risk communication:** SmPC: Section 4.2, Section 4.3, Section 4.4, Section 4.8 PL: Section 2, Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 provides specific instructions on the proper administration of the drug, including: • Caution that aseptic technique must be strictly observed during preparation and administration. • Following Brineura infusion, a calculated amount of flushing solution must be used to flush the infusion components, including the ICV access device, in order to fully administer Brineura and to maintain patency of the ICV access device. • Periodically inspect the infusion system during the infusion for signs of leakage or delivery failure SmPC Section 4.3 states that Brineura must not be administered as long as there are signs of acute ICV access device leakage, device failure, or device-related infection.

Safety Concern	Routine Risk Minimisation Activities
	SmPC Section 4.4 states that healthcare professionals should inspect the scalp for skin integrity to ensure the intracerebroventricular access device is not compromised prior to each infusion. Inspection of the infusion site and a patency check must be performed to detect intracerebroventricular access device leakage and/or failure prior to initiation of Brineura infusion. Consultation with a neurosurgeon may be needed to confirm the integrity of the device. Brineura treatment should be interrupted in cases of device failure and may require replacement of the access device prior to subsequent infusions. CSF samples should routinely be sent for testing to detect subclinical device infections (SmPC Section 4.4, PL Section 2) **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.
Convulsion-Related Adverse Drug Reactions	**Routine risk communication:** SmPC: Section 4.8 PL: Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.
Meningitis	**Routine risk communication:** SmPC: Section 4.2, Section 4.3, Section 4.4, Section 4.8 PL: Section 2, Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Brineura must be administered using aseptic technique to reduce the risk of infection (SmPC Section 4.2 and Section 4.4) and CSF samples should routinely be sent for testing to detect subclinical device infections (SmPC Section 4.4, PL Section 2) **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.
Cardiac Events/ Bradycardia	**Routine risk communication:** SmPC: Section 4.4, Section 4.8 PL: Section 4.

Safety Concern	Routine Risk Minimisation Activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 advises that electrocardiogram (ECG) monitoring during infusion should be performed in patients with a history of bradycardia, conduction disorder, or with structural heart disease, as some patients with CLN2 disease may develop conduction disorders or heart disease. In cardiac normal patients, regular 12-lead ECG evaluations should be performed every 6 months. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.
Hydrocephalus	**Routine risk communication:** SmPC: Section 4.4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.
Long Term Safety and Tolerability	**Routine risk communication:** SmPC: Section 4.8 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.
Use in Pregnancy and During Lactation	**Routine risk communication:** SmPC: Section 4.6 PL: Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.6 states that breastfeeding should be discontinued during treatment with Brineura. **Other routine risk minimisation measures beyond the Product Information:**

Safety Concern	Routine Risk Minimisation Activities
	Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.
Use in Patients Below 2 Years of Age	**Routine risk communication:** SmPC: Section 4.2 PL: Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.
Use in Patients Above 8 Years of Age	**Routine risk communication:** SmPC: Section 4.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.
Use in Patients with Advanced CLN2 Disease	**Routine risk communication:** SmPC: Section 4.4 PL: Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.

V.2: Additional Risk Minimisation Measures

Dosing and Administration Guide

The Dosing and Administration guide is an additional risk minimization measure for the important identified risks of Device Issues (Device Infection/Blockage/Dislocation/ Degradation) and Meningitis.

Objectives:

To provide health care professionals and patients information regarding the proper storage, preparation, and administration of cerliponase alfa.

Rationale for the additional risk minimisation activity:

As cerliponase alfa should be administered via a specific route (ICV), a detailed guide on the steps needed for proper preparation, dosage, storage, and administration of the drug is required to identify and address device related issues: infection including meningitis, blockage, dislocation, and degradation.

Target audience and planned distribution path:

Healthcare professionals:

Dosing and administration guide will provide:

- Instructions for storage, preparation administration, and disposal of the cerliponase alfa
- Guidance on proper dosage (posology) of cerliponase alfa and dose adjustments as needed
- Guidance on device compatibility
- Information on device-related complications, clinical, and laboratory monitoring
- Healthcare professionals are trained on the material in the Dosing and administration guide prior to drug supplied to the site for use.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness of cerliponase alfa labelling and education will be measured by monitoring effectiveness data, the rate and nature of all reported adverse events, and prescribing patterns to verify proper usage of cerliponase alfa in the post-marketing surveillance. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of cerliponase alfa and presented in the PBRER.

Removal of Additional Risk Minimisation Activities

Not applicable.

V.3: Summary of Risk Minimisation Measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation measures	Pharmacovigilance Activities
Hypersensitivity Reactions (Including Anaphylactic Reactions)	Routine risk minimisation measures: SmPC: Section 4.2, Section 4.4, Section 4.8 PL: Section 2, Section 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: Dosing and Administration Guide to HCPs	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: FU: Specific adverse reaction follow-up questionnaire (Non-Clinical Trial Infusion Associated Reaction Form) Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study
Device Issues (Device Infection / Blockage / Dislocation / Degradation)	Routine risk minimisation measures: SmPC: Section 4.2, Section 4.3, Section 4.4, Section 4.8 PL: Section 2, Section 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: Dosing and Administration Guide to HCPs	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire (Request for Additional Information Regarding a Report of Device Related AE Form) Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study
Convulsion-Related Adverse Drug Reactions	Routine risk minimisation measures: SmPC: Section 4.8 PL: Section 2 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study

	Additional risk minimisation measures: None	
Meningitis	Routine risk minimisation measures: SmPC: Section 4.2, Section 4.3, Section 4.4, Section 4.8 PL: Section 2, Section 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: Dosing and Administration Guide to HCPs	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire (Request for Additional Information Regarding a Report of Device Related AE Form) Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study
Cardiac Events/ Bradycardia	Routine risk minimisation measures: SmPC: Section 4.4, Section 4.8 PL: Section 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study
Hydrocephalus	Routine risk minimisation measures: SmPC: Section 4.4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study

Long Term Safety and Tolerability	Routine risk minimisation measures: SmPC: Section 4.8 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study
Use in Pregnancy and During Lactation	Routine risk minimisation measures: SmPC: Section 4.6 PL Section 2 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire (Pregnancy Form) Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study
Use in Patients Below 2 Years of Age	Routine risk minimisation measures: SmPC: Section 4.2, PL: Section 2 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study
Use in Patients Above 8 Years of Age	Routine risk minimisation measures: SmPC Section 4.2 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study

	only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None	
Use in Patients with Advanced CLN2 Disease	Routine risk minimisation measures: SmPC: Section 4.4 PL: Section 2 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of Risk Management Plan for Brineura (cerliponase alfa)

This is a summary of the risk management plan (RMP) for Brineura. The RMP details important risks of Brineura, how these risks can be minimised, and how more information will be obtained about Brineura's risks and uncertainties (missing information).

Brineura's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Brineura should be used.

This summary of the RMP for Brineura should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Brineura's RMP.

I. The medicine and what it is used for

Brineura is authorised for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease (see SmPC for the full indication). It contains cerliponase alfa as the active substance and it is given by intracerebroventricular (ICV) access.

Further information about the evaluation of Brineura's benefits can be found in Brineura's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/brineura

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Brineura, together with measures to minimise such risks and the proposed studies for learning more about Brineura's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Brineura, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Brineura is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks of Brineura are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Brineura. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Hypersensitivity Reactions (Including Anaphylactic Reactions) Device Issues (Device Infection/Blockage/ Dislocation/Degradation) Convulsion-Related Adverse Drug Reactions Meningitis
Important potential risks	Cardiac Events/Bradycardia Hydrocephalus
Important missing information	Long Term Safety and Tolerability Use in Pregnancy and During Lactation Use in Patients Below 2 Years of Age Use in Patients Above 8 Years of Age Use in Patients with Advanced CLN2 Disease

II.B. Summary of important risks

Important identified risk: Hypersensitivity Reactions (Including Anaphylactic Reactions)	
Evidence for linking the risk to the medicine	Hypersensitivity reactions are not unanticipated with any exposure to a protein-based medicinal product. Hypersensitivity reactions have been reported in patients exposed to cerliponase alfa in clinical studies (190-201/202and 190-203). Most of the events were observed during or within 24 hours after completion of infusion suggesting that these reactions are likely related to the cerliponase alfa treatment.
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.2, Section 4.4, Section 4.8 PL: Section 2, Section 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: Dosing and Administration guide to HCPs
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study See section II.C of this summary from an overview of the post-authorisation development plan.

Important identified risk: Device Issues (Device Infection/Blockage/Dislocation/Degradation)	
Evidence for linking the risk to the medicine	Cerliponase alfa should be administered intraventricularly via an implanted ICV reservoir. As with any neurosurgical device, issues with the ICV device such as infection, blockage, and dislocation etc. are known to occur. Device issues, including infection, have been observed in patients exposed to cerliponase alfa in clinical studies (190-201/202and 190-203).
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.2, Section 4.3, Section 4.4, Section 4.8 PL: Section 2, Section 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: Dosing and Administration Guide to HCPs

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study See section II.C of this summary from an overview of the post-authorisation development plan.

Important identified risk: Convulsion-Related Adverse Drug Reactions	
Evidence for linking the risk to the medicine	Convulsions are a common manifestation of CLN2 disease and are expected to occur in this population. Convulsions were reported in 31 (81.5%)of 38 patients exposed to cerliponase alfa in clinical studies (190-201/202 and 190-203). The majority (>90%) of these events were mild to moderate, and 3.5% were considered related to cerliponase alfa.
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.8 PL: Section 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study See section II.C of this summary from an overview of the post-authorisation development plan.

Important identified risk: Meningitis	
Evidence for linking the risk to the medicine	Cerliponase alfa should be administered intraventricularly via an implanted ICV reservoir. As with any neurosurgical device, there is a potential for inflammation of the meninges due to infectious agents. ICV access device-related infections, including sub-clinical infections and meningitis, have been observed in patients treated with Brineura. Meningitis may present with the following symptoms: fever, headache, neck stiffness, light sensitivity, nausea, vomiting, and change in mental status. CSF samples should routinely be sent for testing to detect subclinical device infections. In clinical studies, antibiotics were administered, the ICV access device was replaced, and Brineura treatment was continued.
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.2, Section 4.3, Section 4.4, Section 4.8 PL: Section 2, Section 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: Dosing and Administration Guide to HCPs
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study See section II.C of this summary from an overview of the post-authorisation development plan.

Important potential risk: Cardiac Events/Bradycardia	
Evidence for linking the risk to the medicine	Cardiac events were observed with cerliponase alfa during clinical studies (190-201/202 and 190-203). These included cardiac events such as bradycardia and vascular disorders such as hypotension. No correlation has been observed between cardiac events or bradycardia and safety or efficacy measures in the cerliponase alfa clinical studies. Hence these events were considered as a potential risk for cerliponase alfa.
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4, Section 4.8 PL: Section 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study See section II.C of this summary from an overview of the post-authorisation development plan.

Important potential risk: Hydrocephalus	
Evidence for linking the risk to the medicine	Cerliponase alfa should be administered intraventricularly via an implanted ICV reservoir. As with any neurosurgical device, there is a potential for development of hydrocephalus (communicating or non-communicating) due to the ICV device. No events of hydrocephalus were reported in clinical studies (190-201/202 and 190-203). Cumulatively, as of 26 April 2022, two events of hydrocephalus were reported in the post-marketing setting.
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study See section II.C of this summary from an overview of the post-authorisation development plan.

Important missing information: Long Term Safety and Tolerability	
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.8 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study See section II.C of this summary from an overview of the post-authorisation development plan.

Important missing information: Use in Pregnancy and Lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6, PL: Section 2 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study See section II.C of this summary from an overview of the post-authorisation development plan.

Important missing information: Use in Patients Below 2 Years of Age	
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.2 PL: Section 2 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study See section II.C of this summary from an overview of the post-authorisation development plan.

Important missing information: Use in Patients Above 8 Years of Age	
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.2 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study See section II.C of this summary from an overview of the post-authorisation development plan.

Important missing information: Use in Patients with Advanced CLN2 Disease	
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 PL: Section 2 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Brineura must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 190-504: Cerliponase Alfa Observational Study See section II.C of this summary from an overview of the post-authorisation development plan.

II.C. Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following study is a condition of the marketing authorisation:

Study Short Name: 190-504 (EU): Cerliponase Alfa Observational Study (PASS Study)

Purpose of the study: The primary objective of this non-interventional post authorisation safety (PASS) study is to evaluate the long-term safety of cerliponase alfa in patients with neuronal ceroid lipofuscinosis Type 2 (CLN2 disease).

The secondary objectives of this study include the following:

- To further assess the occurrence of serious hypersensitivity reactions (including anaphylactic reactions), serious cardiovascular adverse events, and serious device-related complications
- To evaluate the effects of Grade III serious adverse events (SAEs) on patient performance on the CLN2 Clinical Rating Scale (Motor and Language domains)

II.C.2 Other studies in post-authorisation development plan

There are no other studies in the post-authorization development plan.

ANNEX 4: Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms:

- Infusion-Related Reactions
- Device-Related Adverse Events
- Pregnancy

BIOMARIN

Request for Additional Information Regarding a Report of Infusion Associated Reactions

TO:	*FROM:* BioMarin Pharmacovigilance

Date:

Dear

We received a report of a patient with Infusion Associated Reactions after or while receiving the following BioMarin product:

Patient Initials/Identifier:		Date of Birth or Age:	

If your office did not initially provide this report, it may have been forwarded to us by a patient or caregiver, a sales representative, a Medical Science Liaison, our Medical Communications department, or a Patient Support Program.

If available, we would be very grateful if you could provide the specific information required on the attached form and return the form by e-mail, fax or mail at your earliest convenience. Please complete the applicable sections.

We are seeking additional information about this potential adverse event as part of our surveillance activities and to fulfill regulatory requirements. Please note that the collection of post-marketing safety information on FDA-regulated products is exempt from HIPAA regulations.

Thank you
BioMarin Pharmaceutical, Inc – Pharmacovigilance

BMRN Ref #:

BIOMARIN

Email completed form to: drugsafety@bmrn.com,
Fax completed from to: 415-532-3144 or mail to:
BioMarin, Inc at 105 Digital Drive, Novato, CA 94949

Patient Information

Patient Identifier:	Country:	Date of Birth or Age:

Reporter Information

Name of reporter completing this form **(if other than addressee, provide contact information below)**: Name:		
Phone Number:	Fax Number:	Email Address:

Relevant Drug Exposure History for Patient

Drug Name (generic or trade name)	Route	Dose and Frequency	Start Date/Time	Stop Date/Time (Check if Continued)	Indication
Enter BioMarin drug(s)					
			Date: Time:	☐ Date: Time:	
			Date: Time:	☐ Date: Time:	
Concomitant Drug (any other non-BioMarin drug)					
			Date: Time:	☐ Date: Time:	☐ Pre-medication
			Date: Time:	☐ Date: Time:	☐ Pre-medication
			Date: Time:	☐ Date: Time:	☐ Pre-medication
			Date: Time:	☐ Date: Time:	☐ Pre-medication

BIOMARIN

Description of the signs and symptoms			
☐ Cutaneous symptoms			
Specify:		Site	Severity: ☐ Mild ☐ Moderate ☐ Severe
START: DATE	TIME:	STOP: DATE	TIME:
☐ Cardiovascular symptoms			
Specify:		Site	Severity: ☐ Mild ☐ Moderate ☐ Severe
START: DATE	TIME:	STOP: DATE	TIME:
☐ Respiratory symptoms			
Specify:		Site	Severity: ☐ Mild ☐ Moderate ☐ Severe
START: DATE	TIME:	STOP: DATE	TIME:
☐ Gastrointestinal symptoms			
Specify:		Site	Severity: ☐ Mild ☐ Moderate ☐ Severe
START: DATE	TIME:	STOP: DATE	TIME:

☐ Other Symptoms		
Specify:	Site	Severity: ☐ Mild ☐ Moderate ☐ Severe
START: DATE TIME:	STOP: DATE	TIME:
Time to onset of the symptoms (describe time taken for symptoms to appear following administration of the infusion (eg within X minutes/hours)		
Describe clinical course (include treatment details eg anti-histamine/steroid,oxygen, intravenous fluids if any)		
Number of doses prior to onset of suspected IAR?		

Vital Signs at the time of the event

Date: Time:	Blood Pressure:	Oxygen Saturation:	Heart rate:	Respiratory Rate:	Temperature:
Date: Time:	Blood Pressure:	Oxygen Saturation:	Heart rate:	Respiratory Rate:	Temperature:
Date: Time:	Blood Pressure:	Oxygen Saturation:	Heart rate:	Respiratory Rate:	Temperature:
Date: Time:	Blood Pressure:	Oxygen Saturation:	Heart rate:	Respiratory Rate:	Temperature:

Treatment Details				
Drug Generic/Trade:	Route:	Start Date:	End Date:	❑ On going
Drug Generic/Trade:	Route:	Start Date:	End Date:	❑ On going
Drug Generic/Trade:	Route:	Start Date:	End Date:	❑ On going
Drug Generic/Trade:	Route:	Start Date:	End Date:	❑ On going
Drug Generic/Trade:	Route:	Start Date:	End Date:	❑ On going

Re-introduction information:			
Was drug re-introduced following resolution/improvement of the reported adverse event?			
☐ Yes	☐ No	☐ Unknown	Specify date of re-introduction:
Did the reported adverse event recur following re-introduction of drug therapy?			
☐ Yes	☐ No	☐ Unknown	Specify date of recurrence:
Was drug infusion slowed/temporarily stopped in response to the reported adverse event?			
☐ Yes	☐ No	☐ Unknown	Specify slowed rate of infusion or date of interruption:
Did the reported AE resolve following slowing of infusion/temporary cessation?			
☐ Yes	☐ No	☐ Unknown	Specify date and time of AE resolution:
Did the reported adverse event recur following re-introduction (if temporarily stopped) of drug therapy?			
☐ Yes	☐ No	☐ Unknown	Specify date of recurrence:

Relevant Laboratory/Diagnostic Data		
Test	Date (dd/mm/yyyy)	Result

Relevant Medical History (including any history of atopy, food or seasonal allergies)		
Previous Drug Reaction(s) to non-company products (name suspect drug)	Date	Symptoms

BIOMARIN

Request for Additional Information Regarding a Report of Pregnancy

TO:	*FROM:* BioMarin Pharmacovigilance

Date:

Dear ,

We received a report of a patient who became pregnant after or while receiving the following BioMarin product: ® ( ).

Patient Initials/Identifier:		Date of Birth or Age:	
Note: "Patient" refers to the mother			

If your office did not initially provide this report, it may have been forwarded to us by a patient or caregiver, a sales representative, a Medical Science Liaison, our Medical Communications department, or a Patient Support Program.

If available, we would be very grateful if you could provide the specific information required on the attached form and return the form by e-mail, fax or mail at your earliest convenience. If you previously provided information during the pregnancy, you are receiving this form so that we can obtain information about the outcome of the pregnancy. Please complete the applicable sections.

We are seeking additional information about this potential adverse event as part of our post-marketing surveillance activities and to fulfill regulatory requirements. Please note that the collection of safety information on FDA-regulated products is exempt from HIPAA regulations.

Thank you
BioMarin Pharmaceutical, Inc – Pharmacovigilance

BMRN Ref #:

BIOMARIN

Email completed form to: drugsafety@bmrn.com,
Fax completed from to: 415-532-3144 or mail to:
BioMarin, Inc at 105 Digital Drive, Novato, CA 94949

Patient Information (Note: "Patient" refers to the mother)

Patient Identifier:	Country:	Date of Birth or Age:

Reporter Information

Name of reporter completing this form **(if other than addressee, provide contact information below)**:		
Health Care Provider? ☐ Yes ☐ No Specify:		
Phone Number:	Fax Number:	Email Address:

Pregnancy Report Information

This report is being made as a:
☐ Prospective Report (reported while patient is pregnant) ☐ Retrospective (reported after pregnancy concluded)

☐ Check this box if the pregnant patient is already participating in a BioMarin study?

Relevant Drug Exposure History for Patient

Drug Name (generic or trade name)	Exposure				Route	Dose and Frequency	Start Date	Stop Date (Check if Continued)	Indication
	Prior to Conception	Trimester							
Enter BioMarin drug(s)									
	☐	1 ☐	2 ☐	3 ☐			DD/MM/YYYY	☐	
	☐	☐	☐	☐			DD/MM/YYYY	☐	
Concomitant Drug (any other non-BioMarin drug)									
	☐	☐	☐	☐			DD/MM/YYYY	☐	
	☐	☐	☐	☐			DD/MM/YYYY	☐	
	☐	☐	☐	☐			DD/MM/YYYY	☐	
	☐	☐	☐	☐			DD/MM/YYYY	☐	

Relevant Medical Procedures for Patient (e.g. ultrasound, amniocentesis, etc.)

Test	Date(s) Performed	Result(s)/Values
	DD/MM/YYYY	
	DD/MM/YYYY	
	DD/MM/YYYY	

BIOMARIN

Relevant Medical History of Patient (Check all that apply)

Contraception	Pregnancy History	Infections/Conditions Present During Current Pregnancy	Exposure Pre- OR During Current Pregnancy
☐ Unknown ☐ None ☐ Oral Contraception ☐ Condom ☐ Diaphragm ☐ IUD ☐ Vasectomy ☐ Tubal Ligation ☐ Spermacide ☐ Progestin Injection/Implant ☐ Withdrawal ☐ Abstinence ☐ Other- **Specify:**	_____ Pregnancies _____ Live Births _____ Spontaneous Abortions/ Miscarriages _____ Induced Abortions _____ Stillbirths _____ Child born with birth defects **Specify:** ☐ Other – **Specify**:	☐ Asthma ☐ Diabetes Mellitus ☐ High Blood Pressure ☐ Epilepsy/Seizures ☐ CMV ☐ Hepatitis B ☐ Toxoplasmosis ☐ P.Carinii ☐ Pneumonia ☐ Rubella ☐ STD – **Specify**: ☐ Other – **Specify:**	☐ Alcohol ☐ Tobacco ☐ Cocaine ☐ Iodine ☐ Tetracycline ☐ Phenytoin ☐ Isotretinoin (Accutane) ☐ Valproic Acid ☐ Warfarin ☐ Folate supplement ☐ Methadone ☐ IV Drug use ☐ Other – **Specify:**

Current Pregnancy Information

1st Day of Last Menstrual Period DD/MM/YYYY	Estimated Date of Conception DD/MM/YYYY	Estimated Date of Delivery DD/MM/YYYY

Current Pregnancy Status (at time of report)

☐ Pregnancy Ongoing
☐ Live Birth (**Please complete Delivery Information Section Below**)
☐ Lost to Follow-Up
☐ Unknown
☐ Ectopic Pregnancy
☐ Spontaneous Abortion/Miscarriage
Date DD/MM/YYYY Trimester:_____
Specify Details:

☐ Stillbirth
Date DD/MM/YYYY Trimester:_____
Specify Details:

☐ Induced Abortion
Date DD/MM/YYYY Trimester:_____
Specify Details:

BIOMARIN

Delivery Information ☐ **Not Applicable (State Reason in "Current Pregnancy information" Section)**

Delivery Date: DD/MM/YYYY	**Delivery Type**: ☐Premature ☐Pre-Term ☐Term ☐Vaginal ☐Scheduled C-Section ☐Emergency C-Section

Infant Information

Infant Outcome: ☐Normal Infant ☐Lost to Follow-Up ☐Unknown

☐ Birth Defect –
Specify Details:

☐ Other– (e.g. fetal distress, any supportive care required at birth, etc)
Specify Details:

Infant Sex: ☐M ☐F ☐Unknown	Infant Identifiers:	Date of Birth: DD/MM/YYYY	Gestational Weeks at Birth:	Apgar Score (0-10 at 10 minutes):

Head circumference: cm / inches	Weight: kg / lbs	Height: cm / inches

If multiple births (i.e. twins), Indicate total #:
Please provide information for infant #1 above, provide information for all other infants in the additional details section below.

Additional details on course of pregnancy, fetal complications, labor and delivery, infant information, etc:

ADVERSE REPORTING FORM Fax completed form to 415-532-3144 or email drugsafety@bmrn.com or mail to BioMarin at 105 Digital Drive, Novato, Ca 94949	BioMarin Case Number:	BIOMARIN

Request for Additional Information Regarding a Report of an Adverse Event

TO:	FROM: BioMarin Pharmacovigilance 415-532-3144 drugsafety@bmrn.com

Date:

Dear ,

BioMarin Pharmacovigilance has received a report of a patient who experienced an adverse event of _____ while being treated with the following BioMarin product: BMN 190 (cerliponase alfa). In our effort to comply with safety reporting requirements, we would like to obtain additional information concerning this event.

Patient Initials:		Date of Birth:	
Patient Gender:	☐ Male ☐ Female	Age:	

Your office may not have provided this report. This report may have been submitted by a patient or caregiver, a sales representative, a Medical Science Liaison, our Medical Communications department, a specialty pharmacy or a Patient Support Program.

If available, we would be very grateful if you could provide the specific information required on the attached form and return the form by email, fax or mail at your earliest convenience.

Please note that the collection of safety information on FDA-regulated products is exempt from HIPAA regulations.

Thank you
BioMarin Pharmaceutical, Inc – Pharmacovigilance

ADVERSE REPORTING FORM Fax completed form to 415-532-3144 or email drugsafety@bmrn.com or mail to BioMarin at 105 Digital Drive, Novato, Ca 94949	BioMarin Case Number:	BIOMARIN

PATIENT AND SUSPECT MEDICATION INFORMATION

Patient initials:	Sex: ☐ M ☐ F	Birth Date:	Age:	Weight:

☐ BMN 190 Indication:_____ Dose:_____ Route:_____ Frequency:_____ Start Date:

_____ Lot Number (if known):_____ Exp. Date:_____ Time from last dose to event onset: _____

Min _____Days

ADVERSE EVENT INFORMATION

Onset Date:_____ Provide a diagnosis and/or Signs and Symptoms:

Describe the event(s) and clinical course:

Adverse Event Seriousness(check only what applies): ☐ Fatal (Date:_____ (dd/MMM/yyyy) ☐ Life Threatening
☐ Required/Prolonged hospitalization ☐ Severe/Permanent Disability ☐ Is a congenital anomaly in child of patient

Event Status at time of this report:
☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Recovered with sequelae: Describe sequelae:_____

Could underlying medical conditions, other medications, or other factors account for the adverse event:
☐ Probably ☐ Possibly ☐ Unlikely ☐ No Explain:

HCP Assessment: Event Related to Suspect Medication? ☐ Yes ☐ No **Event Device Related?** ☐ Yes ☐ No

Action taken with suspect medication:
☐ No Change ☐ Dose Decreased ☐ Dose Held ☐ Dose Increased ☐ Withdrawn ☐ Not Applicable ☐ Unknown

Relevant Diagnostic Test Results : ☐ None

Relevant Concomitant Medications: ☐ None
Name: Indication: Dose: Therapy dates:

Reporter Information: ☐ MD ☐ Nurse ☐ Pharmacist ☐ Other: _____

Name:_____ Date of Report: _____(dd/MMM/yyyy)

Phone:_____ Fax:_____ email:_____

Address: _____

City:_____ ST:_____ Zip:_____

Form completed on behalf of reporter by:_____Date:_____

ADVERSE REPORTING FORM Fax completed form to 415-532-3144 or email drugsafety@bmrn.com or mail to BioMarin at 105 Digital Drive, Novato, Ca 94949	BioMarin Case Number:	BIOMARIN

If not related to this device check not applicable and do not complete this page ☐ Not Applicable

Device Kit Number: _____

Device Associated with this Event:

If more than 1 device involved, complete a separate Device Event Reporting Form for each device.

Implantable Device	Product Preparation Device	Infusion Devices
☐ ICV ☐ Reservoir ☐ Catheter	☐ Product Withdrawal Needle ☐ Product Withdrawal Syringe ☐ Flushing Solution Withdrawal Needle ☐ Flushing Solution Withdrawal Syringe	☐ Pump ☐ Syringe ☐ IV Line ☐ Needle ☐ Filter ☐ Extension Tubing Set

Common Device Name: _____ **Manufacturer Name**:_____

Brand Name:_____ Model #: _____ Lot #: _____

Catalog #:_____ Exp. Date:_____

Serial #:_____ UDI #: _____

Operator: ☐ HCP ☐ Patient ☐ Caregiver ☐ Other _____

Location of Event: ☐ Clinic ☐ Home ☐ Other _____

Date Implanted: _____ (dd/MMM/yyyy) N/A ☐ Date Removed: _____ (dd/MMM/yyyy) N/A ☐

Device Returned: ☐ Yes ☐ No

Form completed on behalf of Reporter by: **Date**

ANNEX 6: Details of Proposed Additional Risk Minimisation Activities

Approved key messages of the additional risk minimisation measures

Dosing and Administration Guide:

The full Dosing and Administration Guide is attached to this annex. A summary of contents is provided below.

As cerliponase alfa should be administered via a specific route (ICV), a detailed guide on the steps needed for proper preparation, dosage, storage, and administration of the drug is required to identify and address device related issues: infection including meningitis, blockage, dislocation, and degradation

Healthcare professionals:

Dosing and administration guide will provide:

Instructions for storage, preparation, administration, and disposal of cerliponase alfa

Shelf Life: 2 years

Unopened frozen vials have a shelf life of up to 2 years. Thawed Brineura and flushing solution should be used immediately. Product should only be withdrawn from the unopened vials immediately prior to use. If immediate use is not possible, unopened vials of Brineura or flushing solution should be stored at 2-8°C and used within 24 hours.

Special Precautions for Storage

Store upright in a freezer (-25°C to -15°C).

Special Precautions for Dosing and Administration

Aseptic techniques must be strictly observed during preparation and administration.

Brineura and flushing solution must be administered via the intracerebroventricular route only. Surgical implantation of the intracerebroventricular access device must take place prior to the first infusion.

Posology

The recommended dose is 300 mg cerliponase alfa administered once every other week by intracerebroventricular infusion.

In patients less than 2 years of age, lower doses are recommended, as below.

Age groups	Total dose administered every other week (mg)
Birth to < 6 months	100
6 months to < 1 year	150
1 year to < 2 years	200 (first 4 doses) 300 (subsequent doses)
2 years and older	300

Dose adjustments

Consideration of dose adjustments may be necessary for patients who may not tolerate the infusion. The dose may be reduced by 50% and/or the infusion rate decreased to a slower rate.

If the infusion is interrupted due to a hypersensitivity reaction, it should be restarted at approximately one-half the initial infusion rate at which the hypersensitivity reaction occurred.

The infusion should be interrupted and/or the rate slowed in patients who in the judgement of the treating physician have a possible increase in intracranial pressure during the infusion as suggested by symptoms such as headache, nausea, vomiting, or decreased mental state.

Guidance on proper Method of administration

Preparation for administration of Brineura and Flushing Solution

Thaw Brineura vials and flushing solution vial at room temperature for approximately 60 minutes. **Do not** thaw or warm vials any other way. **Do not** shake vials. Condensation will occur during thawing period. Thawing the vials outside the carton is recommended.

Brineura and flushing solution must be completely thawed and used immediately.

Do not re-freeze vials or freeze syringes containing Brineura or flushing solution.

Inspect thawed Brineura and flushing solution vials

Inspect the vials to ensure they are fully thawed. Brineura and flushing solution should be clear to slightly opalescent and colourless to pale yellow. Brineura vials may occasionally contain thin translucent fibres or opaque particles. These naturally occurring particles are cerliponase alfa. These particles are removed via the 0.2 µm inline filter without having a detectable effect on the purity or strength of Brineura.

The flushing solution may contain particles that dissolve when the vial is fully thawed.

Do not use if the solutions are discoloured or if there is other foreign particulate matter in the solutions.

Withdraw Brineura

Label one unused sterile syringe “Brineura” and attach a syringe needle. Remove the green flip-off caps from both Brineura vials. Using aseptic technique, withdraw the volume of Brineura solution per required dose. Do not dilute Brineura. Do not mix Brineura with any other medicinal product. Discard the needle and empty vials.

Withdraw flushing solution

Determine the volume of flushing solution needed to ensure complete delivery of Brineura to the cerebral ventricles. Calculate the flush volume by adding the priming volume of all infusion components, including the intracerebroventricular access device.

Label one unused sterile syringe “flushing solution” and attach a syringe needle. Remove the yellow flip-off cap from the flushing solution vial. Using aseptic technique, withdraw the appropriate amount of flushing solution from the vial into the new sterile syringe labelled “flushing solution”. Discard the needle and the vial with the remaining solution.

Information on the device-related complications, clinical and laboratory monitoring

Device-related complications

Brineura must be administered using aseptic technique to reduce the risk of infection. In clinical studies, events of intracerebroventricular access device-related infections were observed. In these cases, antibiotics were administered, the intracerebroventricular access device was replaced, and Brineura treatment was continued.

Healthcare professionals should inspect the scalp for skin integrity to ensure the intracerebroventricular access device is not compromised prior to each infusion. Inspection of the infusion site and a patency check must be performed to detect intracerebroventricular access device leakage and/or failure prior to initiation of Brineura infusion. Consultation with a neurosurgeon may be needed to confirm the integrity of the device. Brineura treatment should be interrupted in cases of device failure and may require replacement of the access device prior to subsequent infusions.

In case of intracerebroventricular access device-related complications, refer to the manufacturer’s labelling for further instruction.

Caution should be taken in patients prone to complications from intracerebroventricular medicinal product administration, including patients with obstructive hydrocephalus.

Clinical and laboratory monitoring

Vital signs should be monitored before infusion starts, periodically during infusion, and post-infusion in a healthcare setting. Upon completion of the infusion, the patient status should be clinically assessed and observation may be necessary for longer periods if clinically indicated, particularly in patients less than 3 years.

Electrocardiogram (ECG) monitoring during infusion should be performed in patients with a history of bradycardia, conduction disorder, or with structural heart disease, as some patients with CLN2 disease may develop conduction disorders or heart disease. In cardiac normal patients, regular 12-lead ECG evaluations should be performed every 6 months.

CSF samples should routinely be sent for testing to detect subclinical device infections.

Brineura®▼
(cerliponase alfa)

DOSING & ADMINISTRATION GUIDE

▼This medicinal product is subject to additional monitoring, special reporting is required in relation to adverse reactions.

Getting ready to administer BRINEURA®[1]

BRINEURA® is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency.

The following steps are recommended for the dosing and administration of BRINEURA® and are based on the Summary of Product Characteristics. Please refer to the full Summary of Product Characteristics (provided with this pack), your physician's instructions and your institution's policies and procedures for additional information and guidance.

BRINEURA® must only be administered via the intracerebroventricular route. BRINEURA® must only be administered by a trained healthcare professional knowledgeable in intracerebroventricular administration in a healthcare setting.

Special warnings and precautions for use[1]

Device-related complications

BRINEURA® must be administered using aseptic technique to reduce the risk of infection. In clinical studies, events of intracerebroventricular access device-related infections were observed. In these cases, antibiotics were administered, the intracerebroventricular access device was replaced and BRINEURA® treatment was continued.

Healthcare professionals should inspect the scalp for skin integrity to ensure the intracerebroventricular access device is not compromised prior to each infusion. Inspection of the infusion site and a patency check should be performed to detect intracerebroventricular access device leakage and/or failure prior to initiation of BRINEURA® infusion. Consultation with a neurosurgeon may be needed to confirm the integrity of the device. BRINEURA® treatment should be interrupted in cases of device failure and may require replacement of the access device prior to subsequent infusions.

In case of intracerebroventricular access device complications, refer to the manufacturer's labelling for further instruction.

Caution should be taken in subjects prone to complications from intracerebroventricular medicinal product administration, including patients with obstructive hydrocephalus.

Clinical and laboratory monitoring

Vital signs should be monitored before infusion starts, periodically during infusion, and post-infusion, in a healthcare setting. Upon completion of the infusion, the patient status should be clinically assessed and observation may be necessary for longer periods if clinically indicated, particularly in patients <3 years of age.

Electrocardiogram (ECG) monitoring during infusion should be performed in patients with a history of bradycardia, conduction disorder, or with structural heart disease, as some patients with CLN2 disease may develop conduction disorders or heart disease. In cardiac normal patients, regular 12-lead ECG evaluations should be performed every 6 months.

Cerebrospinal fluid (CSF) samples should routinely be sent for testing to detect subclinical device infections.

Paediatric population

There were no patients with advanced disease progression at treatment initiation who were included in clinical trials and no clinical data is available in children <2 years of age. Patients with advanced CLN2 disease and newborns may have decreased integrity of the blood-brain barrier. Effects of the potentially increased medicinal product exposure on the periphery are unknown.

Sodium content

This medicinal product contains 44 mg sodium per vial of BRINEURA® and flushing solution. This should be taken into consideration for patients on a controlled sodium diet.

Recommended dose[1]

BRINEURA® 150 mg solution for infusion is available in single-use vials, each containing 5 ml of solution. Each ml of solution for infusion contains 30 mg of cerliponase alfa.

The recommended dose is 300 mg (10 ml total from 2 vials) administered once every other week by intracerebroventricular infusion. In patients <2 years of age, lower doses are recommended.

Pre-treatment of patients with antihistamines, with or without antipyretics, is recommended 30 to 60 minutes prior to the start of infusion.

Paediatric population

The safety and efficacy of BRINEURA® in children <3 years of age has not yet been established. Limited data are available for children aged 2 years and no clinical data are available in children <2 years of age. Posology is based on the age of the patients at the time of treatment. In patients <3 years of age the recommended dose is based on an ongoing clinical study. BRINEURA® should be administered according to the following recommended dose once every other week:

- Birth to <6 months: 100 mg
- 6 months to <1 year: 150 mg
- 1 year to <2 years: 200 mg (first 4 doses), 300 mg (subsequent doses)
- ≥2 years: 300 mg

Dose adjustments

Consideration of dose adjustments may be necessary for patients who may not tolerate the infusion. The dose may be reduced by 50% and/or the infusion rate decreased to a slower rate. If the infusion is interrupted due to a hypersensitivity reaction, it should be restarted at approximately one-half the initial infusion rate at which the hypersensitivity reaction occurred.

The infusion should be interrupted and/or the rate slowed in patients who, in the judgement of the treating physician, have a possible increase in intracranial pressure during the infusion as suggested by symptoms such as headache, nausea, vomiting or decreased mental state. These precautions are of particular importance in patients <3 years of age.

Storage and care[1]

One carton of BRINEURA® contains three vials (two vials of BRINEURA® and one vial of flushing solution). Each vial of BRINEURA® and flushing solution is intended for single use only:

- Store upright in a freezer (–25°C to –15°C)
- Store in the original package in order to protect from light
- Unopened frozen vials have a shelf life of up to 2 years, see expiry date on the carton

Before use:

- Vials should be thawed at room temperature for approximately 60 minutes
- It is recommended to thaw vials outside the carton. Condensation will occur during the thaw period. **Do not** thaw or warm vials any other way
- **Do not** shake vials
- BRINEURA® and flushing solution must be completely thawed and used immediately. Product should only be withdrawn from the unopened vials immediately prior to use. If immediate use is not possible, unopened vials of BRINEURA® or flushing solution should be stored at 2–~~8~~°C and used within 24 hours
- If open vials or product held in syringes are not used immediately, in-use storage times and conditions prior to use are the responsibility of the user
- **Do not** dilute BRINEURA® or mix with any other medications. **Do not** re-freeze vials or freeze syringes containing BRINEURA® or flushing solution

Prior to administration

Aseptic technique must be strictly observed during preparation and administration.

- BRINEURA® and the flushing solution must only be administered via the intracerebroventricular route
- Surgical implantation of an intracerebroventricular access device (reservoir and catheter) must take place prior to the first infusion
- The implanted intracerebroventricular access device should be appropriate for accessing the cerebral ventricles for therapeutic administration

A number of infusion components are required (but not supplied) – all must be sterile and compatible with BRINEURA® and the flushing solution:

- Refer to BRINEURA® Summary of Product Characteristics section 6.6 for the list of compatible infusion components

Check you have the following sterile components before preparing to administer BRINEURA®:

- A programmable syringe pump with appropriate delivery range, delivery rate accuracy and alarms for incorrect delivery or occlusion. The pump must be programmable to deliver the medicinal product at a constant rate of 2.5 ml/hr. The complete infusion time, including BRINEURA® and the required flushing solution, is administered over approximately 2 to 4.5 hours, depending on the dose and volume administered
- Two single-use drug syringes compatible with the pump equipment. A syringe volume of 10 to 20 ml is recommended
- Two single-use hypodermic syringe needles (21 G, 25.4 mm)
- One single-use infusion set. An extension line may be added if needed. A length of 150 to 206 cm (not to exceed 400 cm) and an inner diameter of 0.1 cm is recommended
- A 0.2 µm inline filter. The inline filter may be integral to the infusion set. The inline filter should be placed as close as practically possible to the port needle
- A non-coring port needle with a gauge of 22 or smaller and a suggested length of 16 mm. Refer to the intracerebroventricular access device manufacturer's recommendation for the port needle
- One empty sterile single-use syringe (for collection of cerebrospinal fluid (CSF) to check patency)

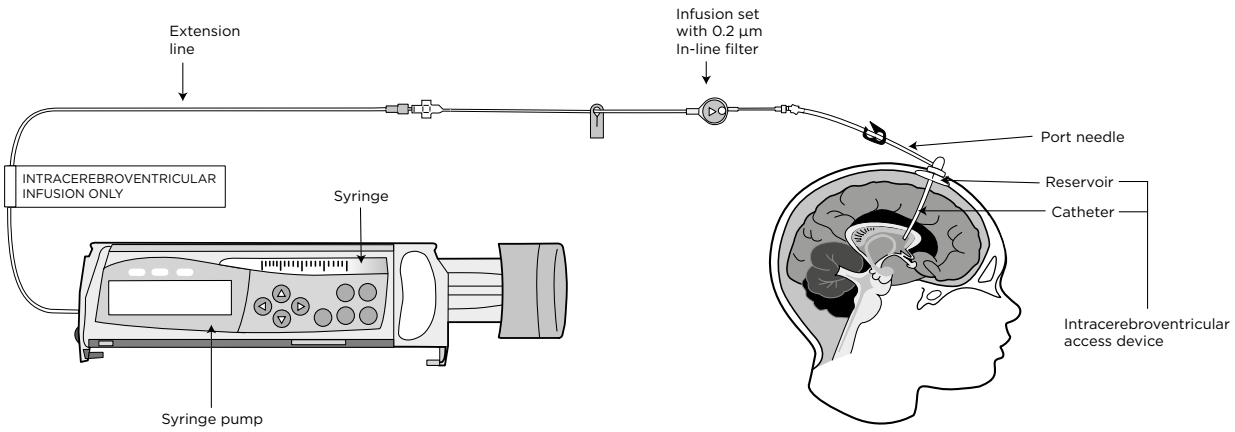

Figure 1: Infusion system set-up

Preparing BRINEURA® and flushing solution

Remove the carton containing two vials of BRINEURA® and one vial of flushing solution from the freezer:

- Vials should be thawed at room temperature for approximately 60 minutes
- It is recommended to thaw vials outside the carton. Condensation will occur during the thaw period. **Do not** thaw or warm vials any other way
- **Do not** shake vials
- BRINEURA® and flushing solution must be completely thawed and used immediately. Product should only be withdrawn from the unopened vials immediately prior to use. If immediate use is not possible, unopened vials of BRINEURA® or flushing solution should be stored at 2–~~8~~°C and used within 24 hours

Inspect all the thawed vials:

- BRINEURA® and the flushing solution should be clear to slightly opalescent and colourless to pale yellow
- BRINEURA® vials may occasionally contain thin translucent fibres or opaque particles. These naturally occurring particles are cerliponase alfa. These particles are removed via the 0.2 µm inline filter without having a detectable effect on the purity or strength of BRINEURA®. The flushing solution may contain particles that dissolve when the vial is fully thawed. **Do not** use if the solutions are discoloured or if there is other foreign particulate matter in the solutions

WITHDRAW BRINEURA®:

- Label one unused sterile syringe 'Brineura' and attach a syringe needle
- Remove green flip-off caps from both BRINEURA® vials
- Using aseptic technique, withdraw the volume of BRINEURA® solution per required dose into the sterile syringe labelled 'Brineura'
- Do not dilute BRINEURA®. Do not mix BRINEURA® with any other medicinal product
- Discard needle and empty vials per local requirements

WITHDRAW FLUSHING SOLUTION:

- Determine the volume of flushing solution needed to ensure complete delivery of BRINEURA® to the cerebral ventricles. Calculate the flush volume by adding the priming volume of all infusion components, including the intracerebroventricular access device
- Label one unused sterile syringe 'flushing solution' and attach a syringe needle
- Remove the yellow flip-off cap from the flushing solution vial
- Using aseptic technique, withdraw the appropriate amount of flushing solution from the vial into the new sterile syringe labelled 'flushing solution'
- Discard needle and vial with remaining solution

Administering BRINEURA®

INTRACEREBROVENTRICULAR INFUSION OF BRINEURA®

Administer BRINEURA® **before** flushing solution.

1. Label the infusion line for 'intracerebroventricular infusion only'
2. Attach the syringe containing BRINEURA® to the extension line, if used, otherwise connect the syringe to the infusion set. The infusion set must be equipped with a 0.2 µm inline filter. See Figure 1 on page 4
3. Prime the infusion components with BRINEURA®
4. Inspect the scalp for signs of intracerebroventricular access device leakage or failure and for potential infections (swelling, erythema of the scalp, extravasation of fluid or bulging of the scalp around or above the intracerebroventricular access device). Do not administer BRINEURA® if there are signs and symptoms of acute intracerebroventriuclar access device leakage, device failure or device-related infection
5. Prepare the scalp for intracerebroventricular infusion using aseptic technique per institution standard of care
6. Insert the port needle into the intracerebroventricular access device
7. Connect a separate empty sterile syringe (no larger than 3 ml) to the port needle. Withdraw 0.5 ml to 1 ml of CSF to check patency of the intracerebroventricular access device
   - **Do not return CSF to the intracerebroventricular access device.** CSF samples should routinely be sent for infection monitoring
8. Attach the infusion set to the port needle (see Figure 1)
   - Secure the components per institution standard of care
9. Place the syringe containing BRINEURA® into the syringe pump and programme the pump to deliver at an infusion rate of 2.5 ml per hour
   - Programme the pump alarms to sound at the most sensitive settings for pressure, rate and volume limits. See the syringe pump manufacturer's operating manual for details
   - **Do not deliver as a bolus or manually**
10. Initiate infusion of BRINEURA® at a rate of 2.5 ml per hour
    - Advise caregivers that movement of the child during the infusion should be kept to a minimum to avoid dislodgement of the needle
11. Periodically inspect the infusion system during the infusion for signs of leakage or delivery failure
12. Verify that the 'Brineura' syringe in the syringe pump is empty after the infusion is complete. Detach and remove the empty syringe from the pump and disconnect from the tubing. Discard the empty syringe in accordance with local requirements

INTRACEREBROVENTRICULAR INFUSION OF FLUSHING SOLUTION

Administer the flushing solution provided **after** BRINEURA® infusion is complete.

1. Attach the syringe containing the calculated volume of flushing solution to the infusion components
2. Place the syringe containing flushing solution into the syringe pump and programme the pump to deliver at an infusion rate of 2.5 ml per hour
   - Programme the pump alarms to sound at the most sensitive settings for pressure, rate and volume limits. See the syringe pump manufacturer's operating manual for details.
   - **Do not deliver as a bolus or manually**
3. Initiate infusion of flushing solution at a rate of 2.5 ml per hour
4. Periodically inspect the infusion components during the infusion for signs of leakage or delivery failure
5. Verify that the 'flushing solution' syringe in the syringe pump is empty after the infusion is complete. Detach and remove the empty syringe from the pump and disconnect from the infusion line
6. Remove the port needle. Apply gentle pressure and bandage the infusion site per institution standard of care
7. Dispose of the infusion components, needles, unused solutions and other waste materials in accordance with local requirements

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or call The Yellow Card Scheme on Freephone: 0808 100 3352 (10 am to 2 pm Monday–Friday only).

Adverse events should also be reported to BioMarin on +1 415 506 6179 or drugsafety@bmrn.com

Reference: 1. BRINEURA® Summary of Product Characteristics.
Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004065/WC500229798.pdf.

EU/BRIN/0033 July 2017